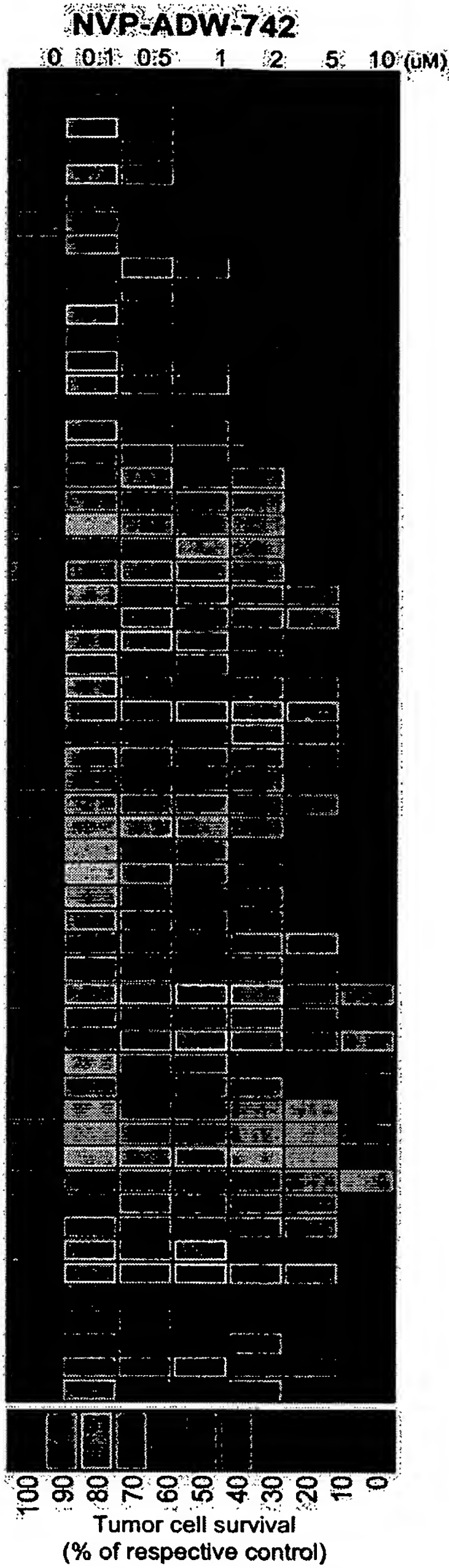


INA-6
ARD
NCI-H929
ARK
L363
MM-1S-Bcl-2
LP-1
MM-1S
MM-1S-myr-Akt
MM-1R
OPM-1
EJM
OCI-MY5
MM-1S-TR-15
KMS-12-BM
RPMI-8226/S
U266
MR20
OCI-MY7
LR5
Brown
Dox40
XG-1
LR5
DHL-10
DHL-4
DHL-7
DHL-8
RL
WM-WSU
GDM-1
HL-60
KG-1a
REH
BHP-10
BHP-17
BHP-2
SW-579
TT
WRO
ARO
FRO
ZR-75-1
MCF-7
MDA-MB-231
PC-3
LNCaP
DU145
786-O
ACHN
SW480
SKOV-3
TC106
TC71
TC268
TC248
WERI



A	Control
B	α IR3
C	NVP-ADW742
D	anti-IL-6R
E	20% serum
F	α IR3+20%serum
G	NVP-ADW742+20%serum
H	anti-IL-6R+20%serum

Figure 2

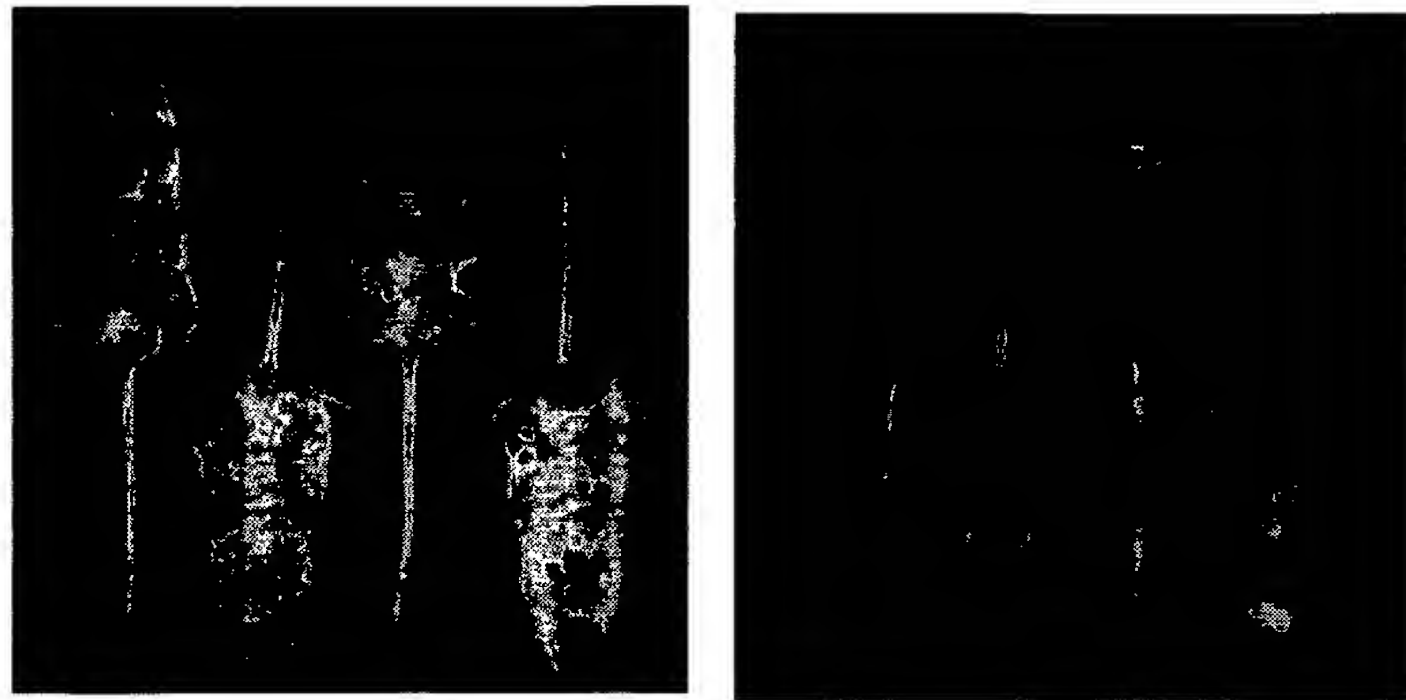
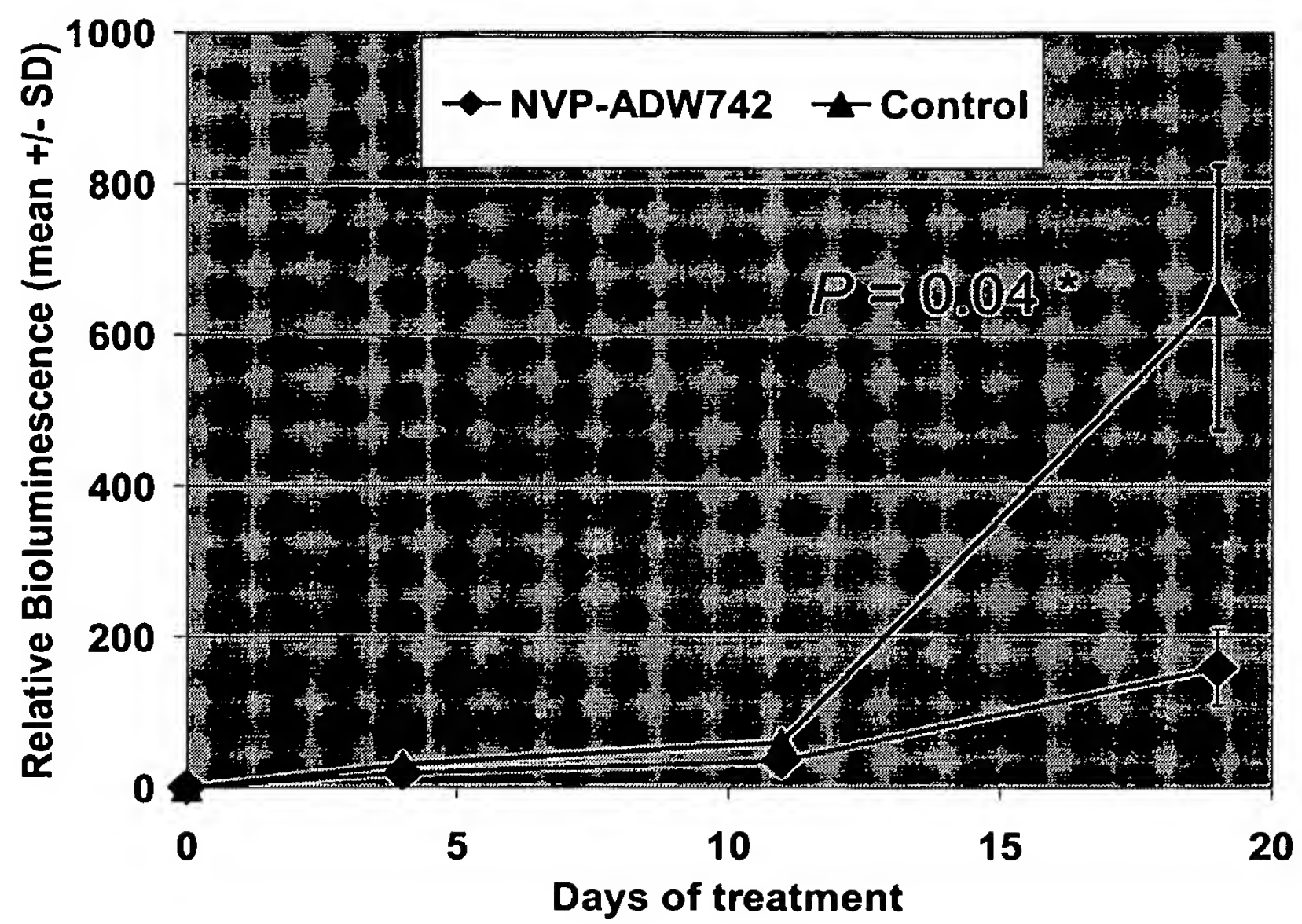
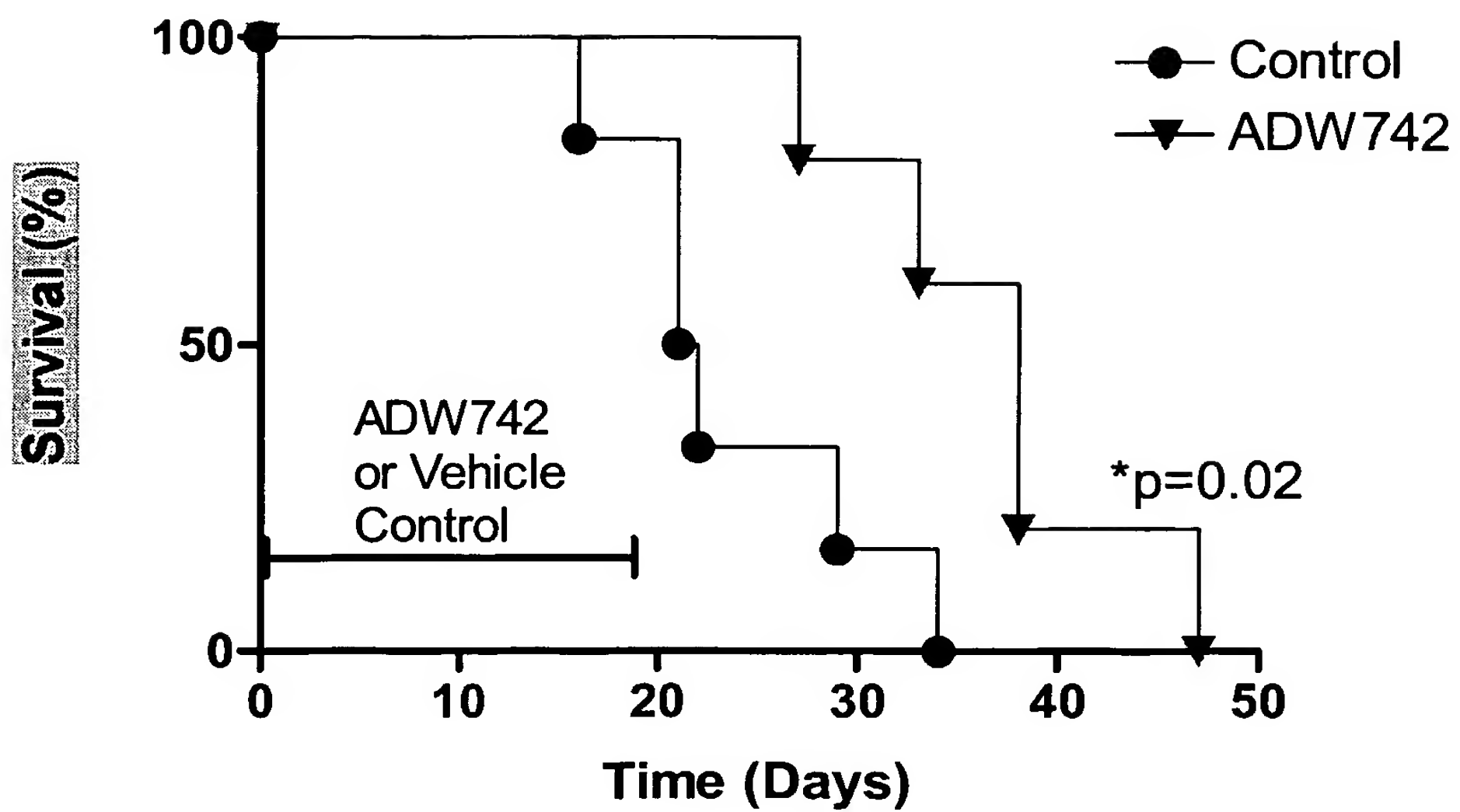
a*b**c*

Figure 3

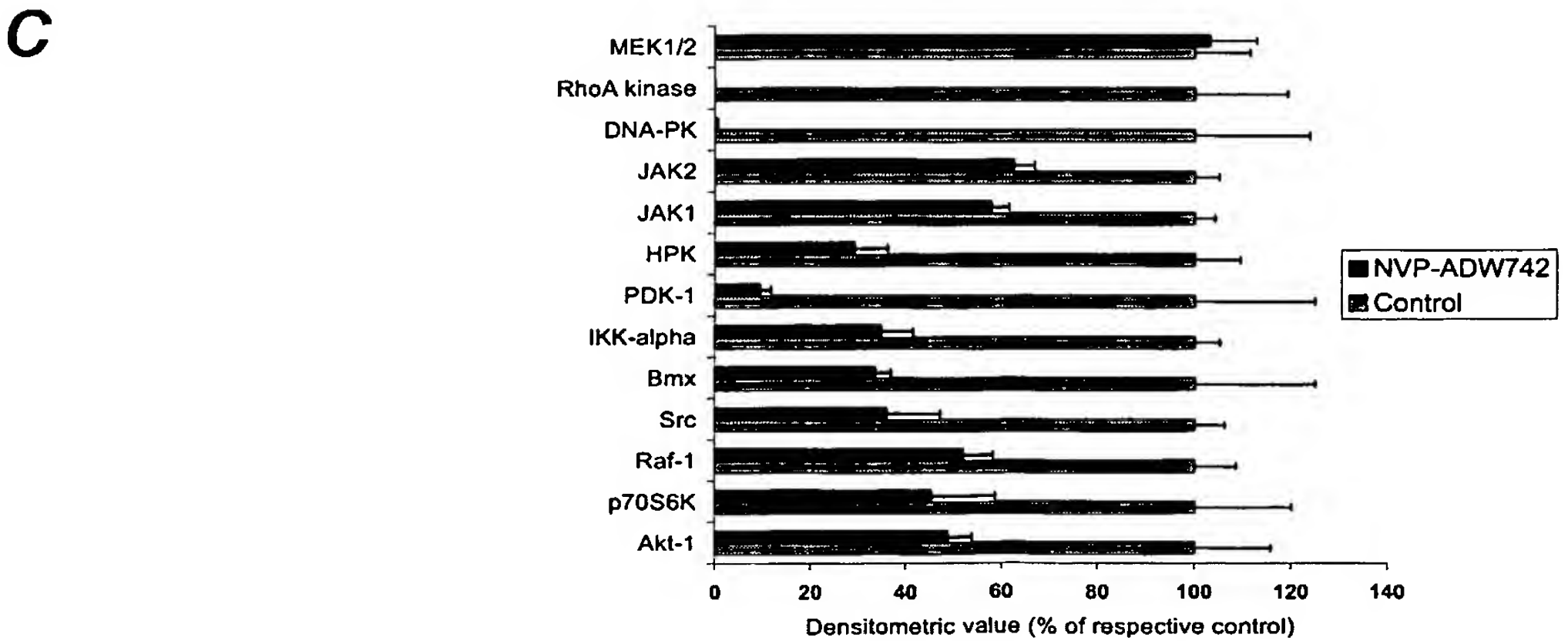
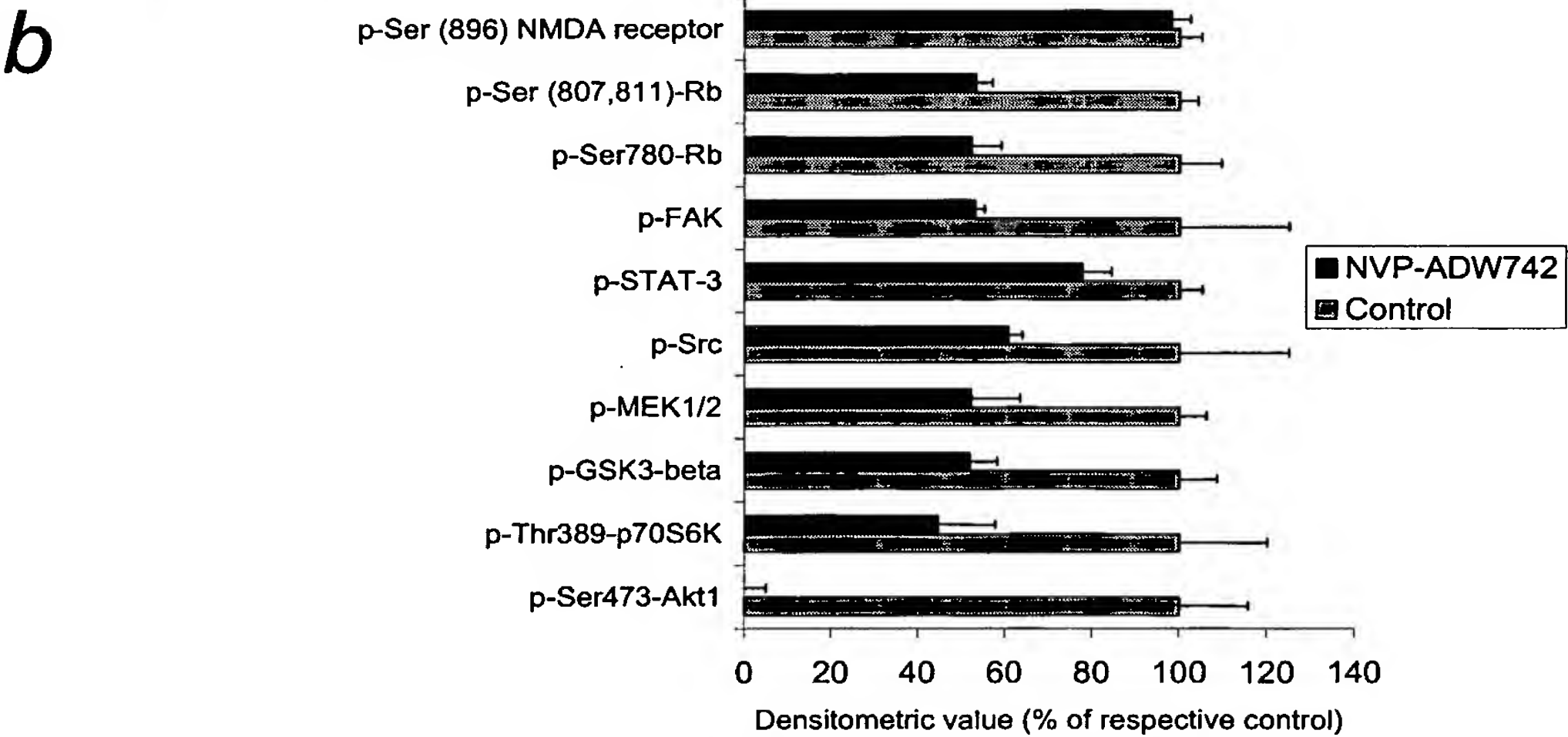
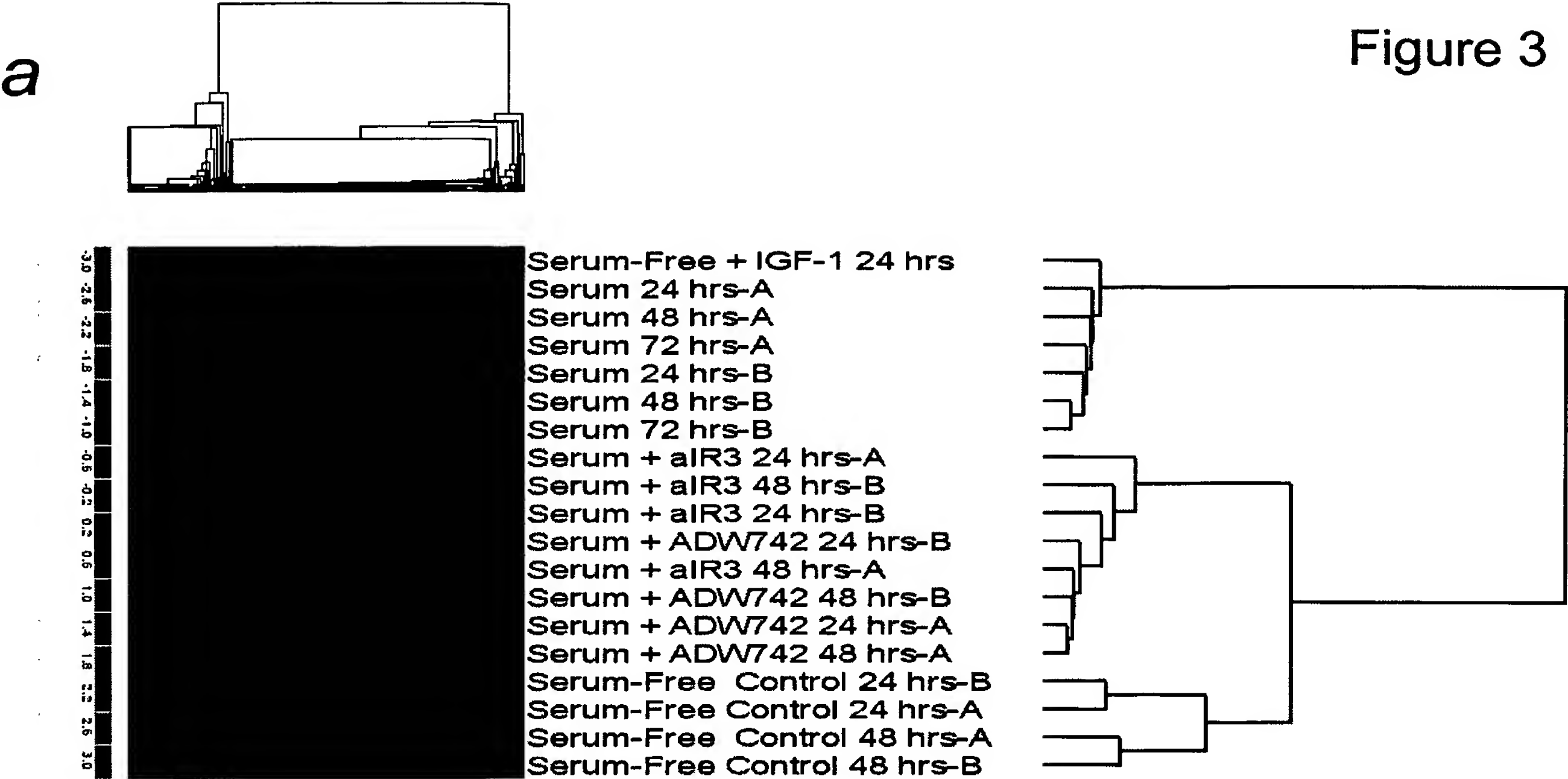


Figure 4

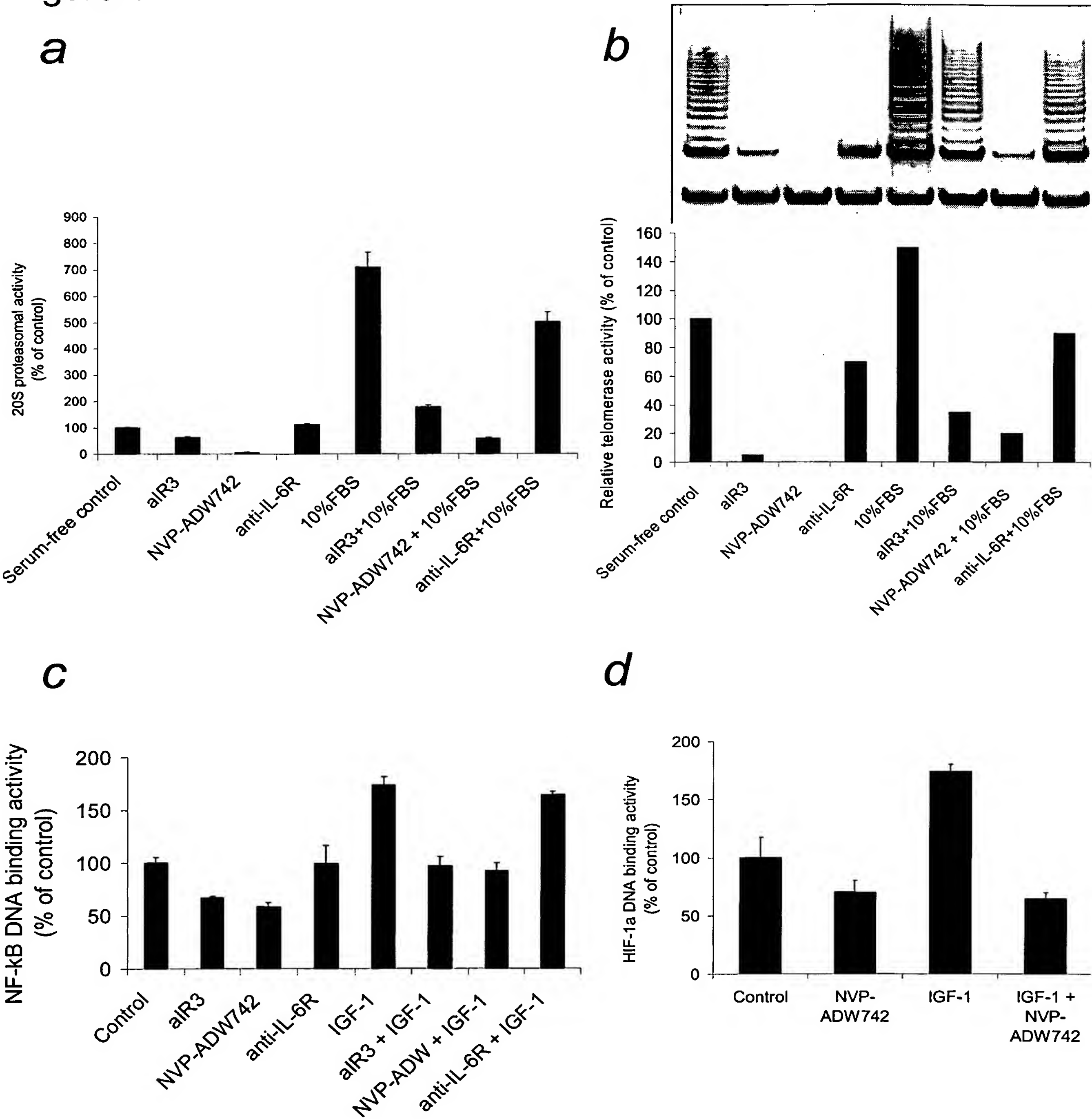


Figure 5

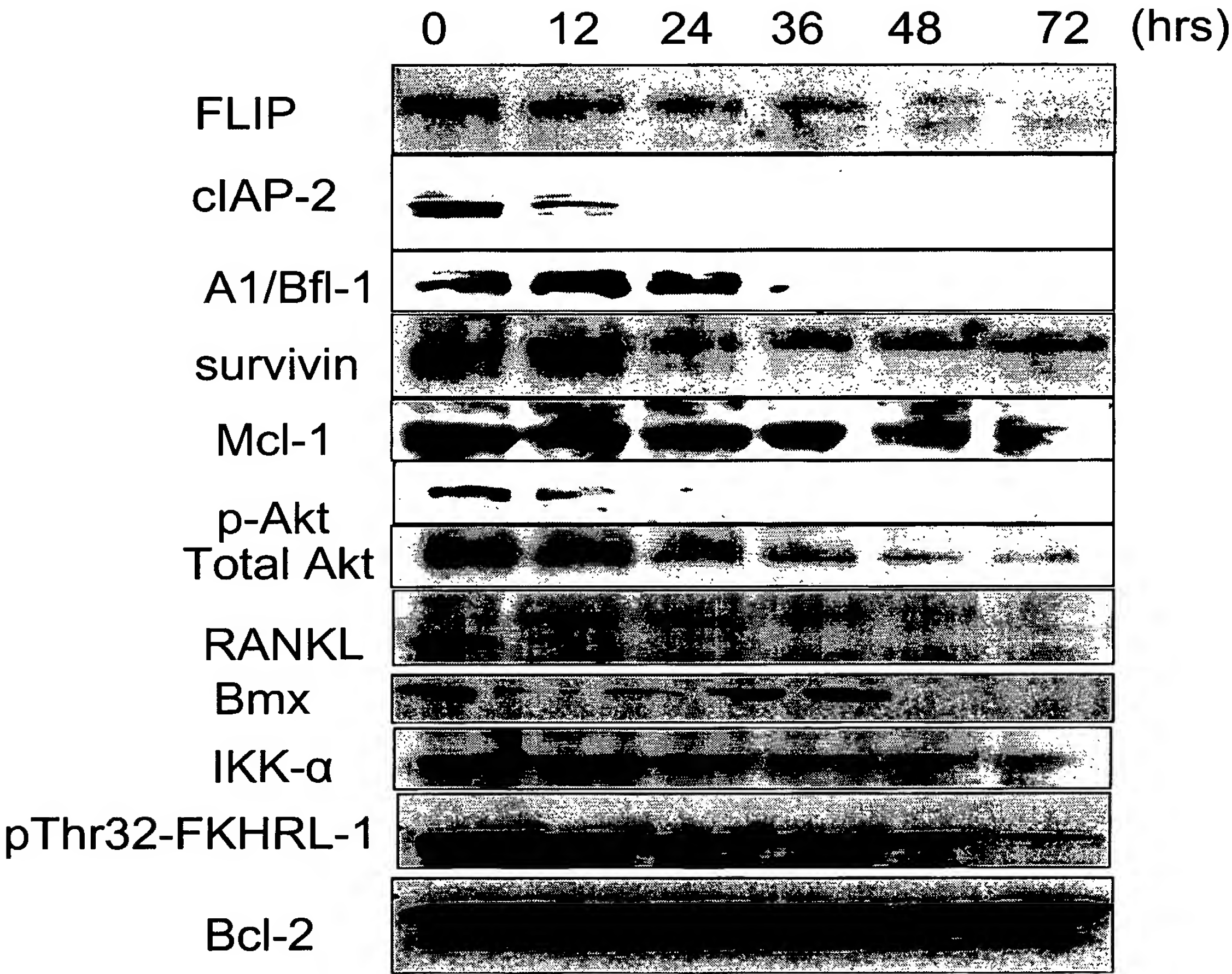


Figure 6

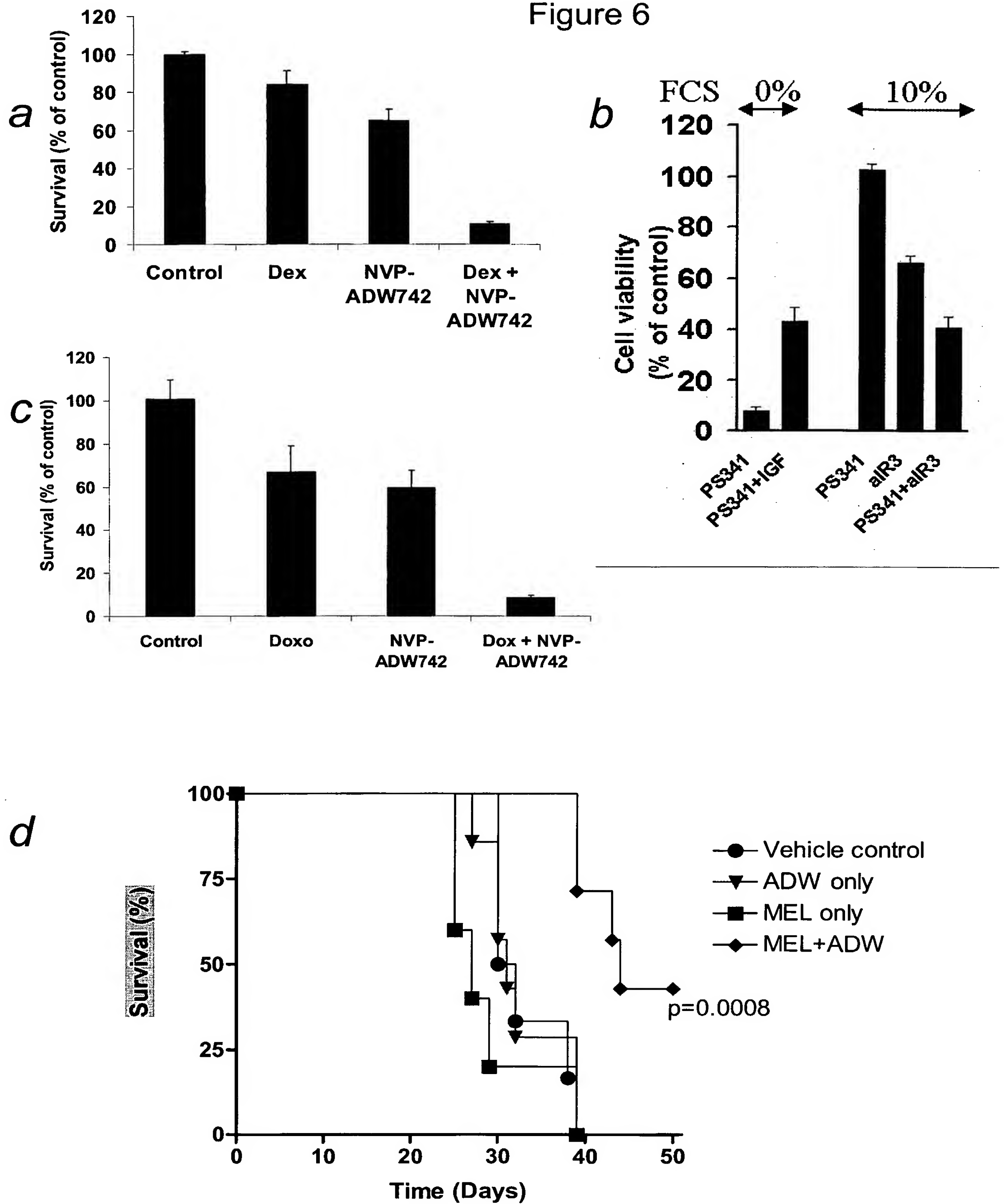
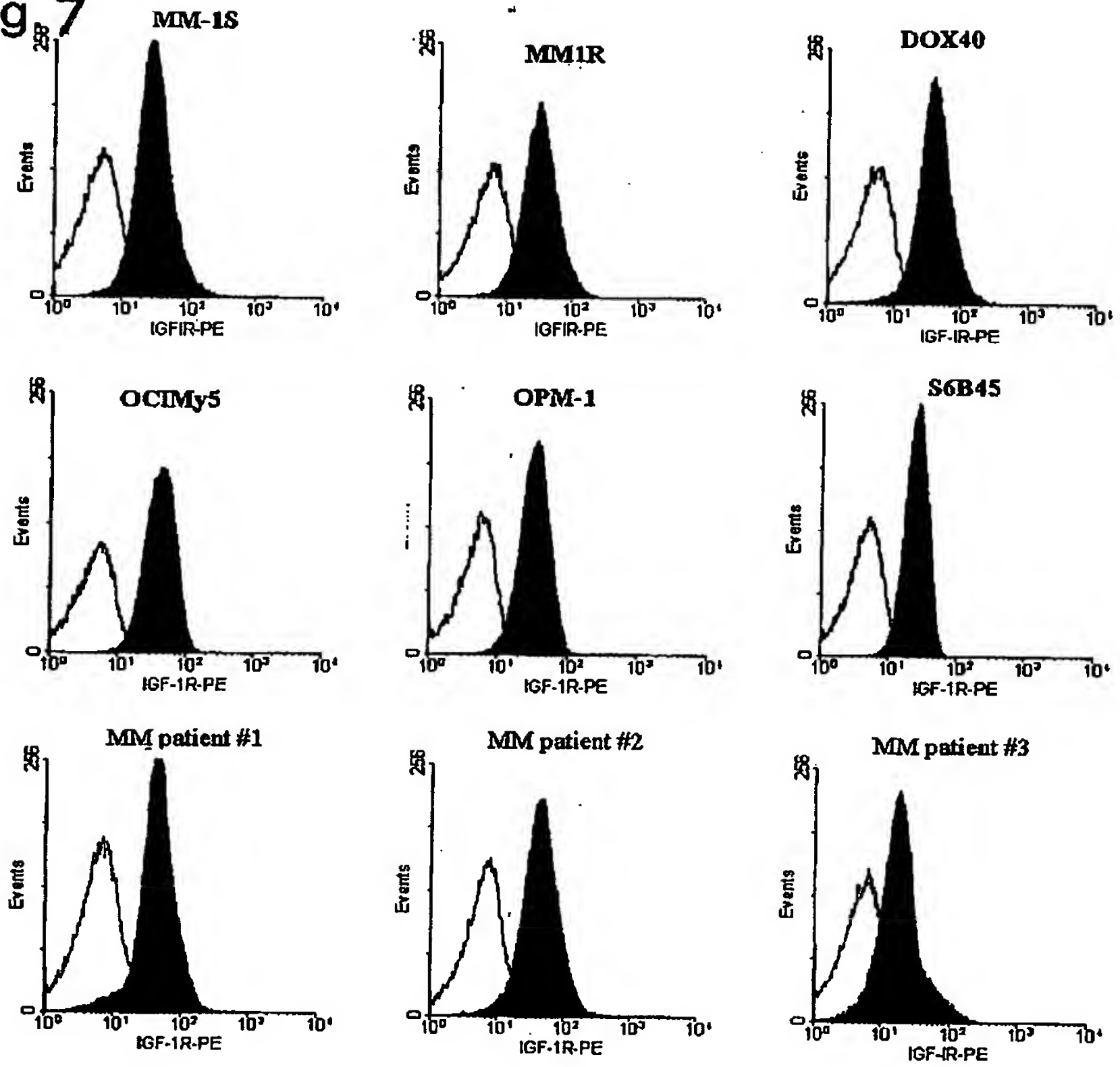
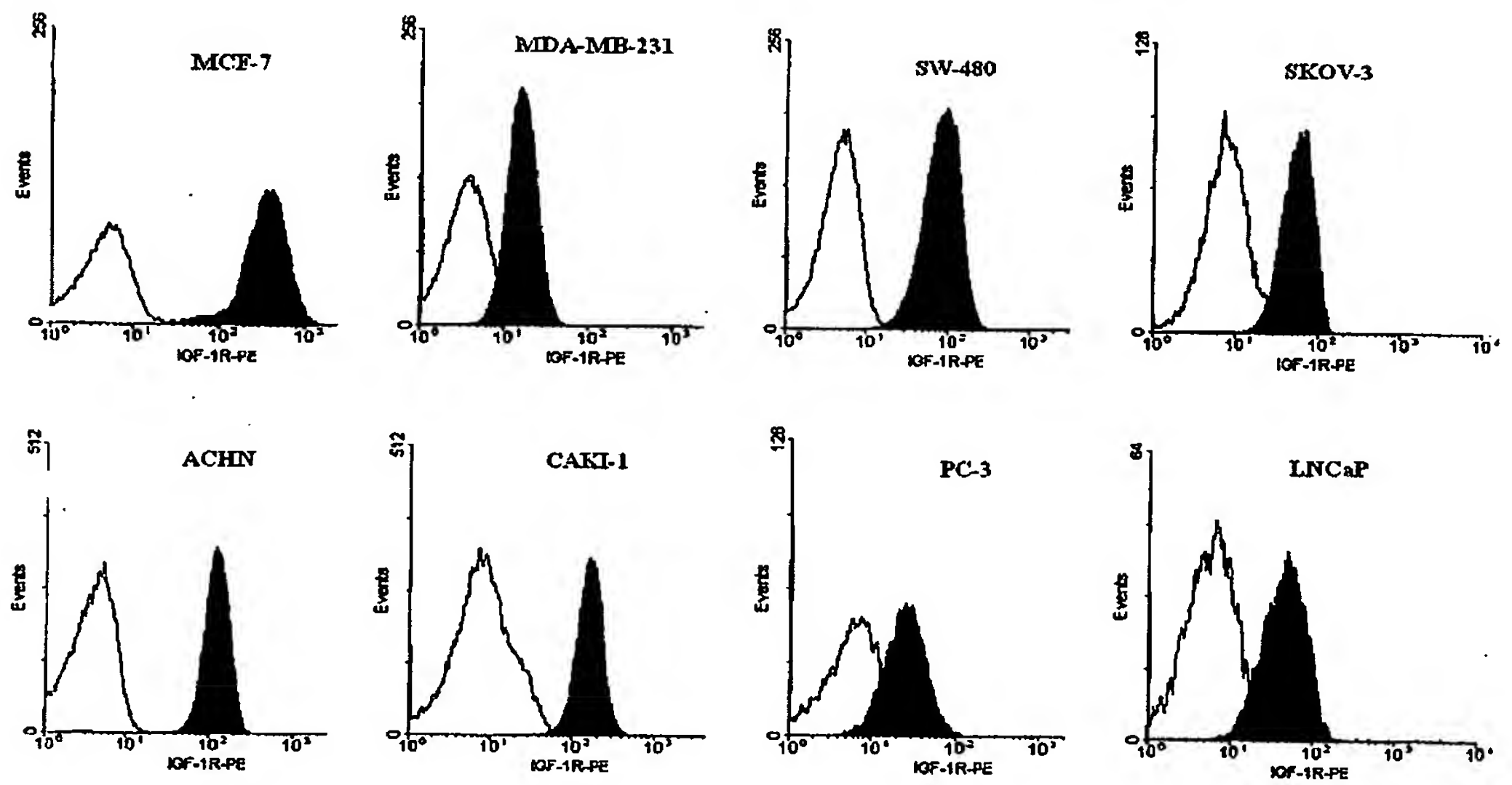


Fig 7

a



b



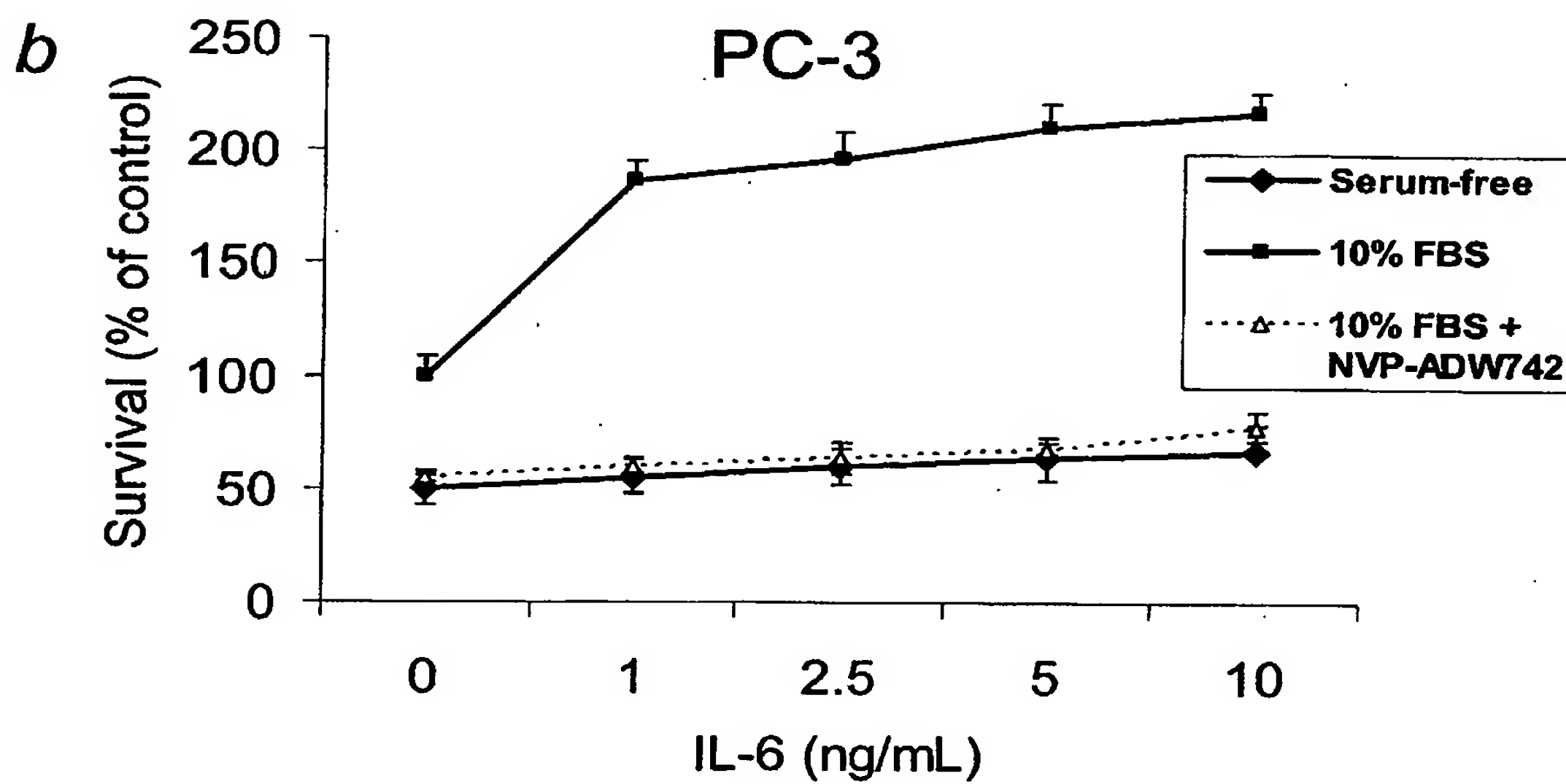
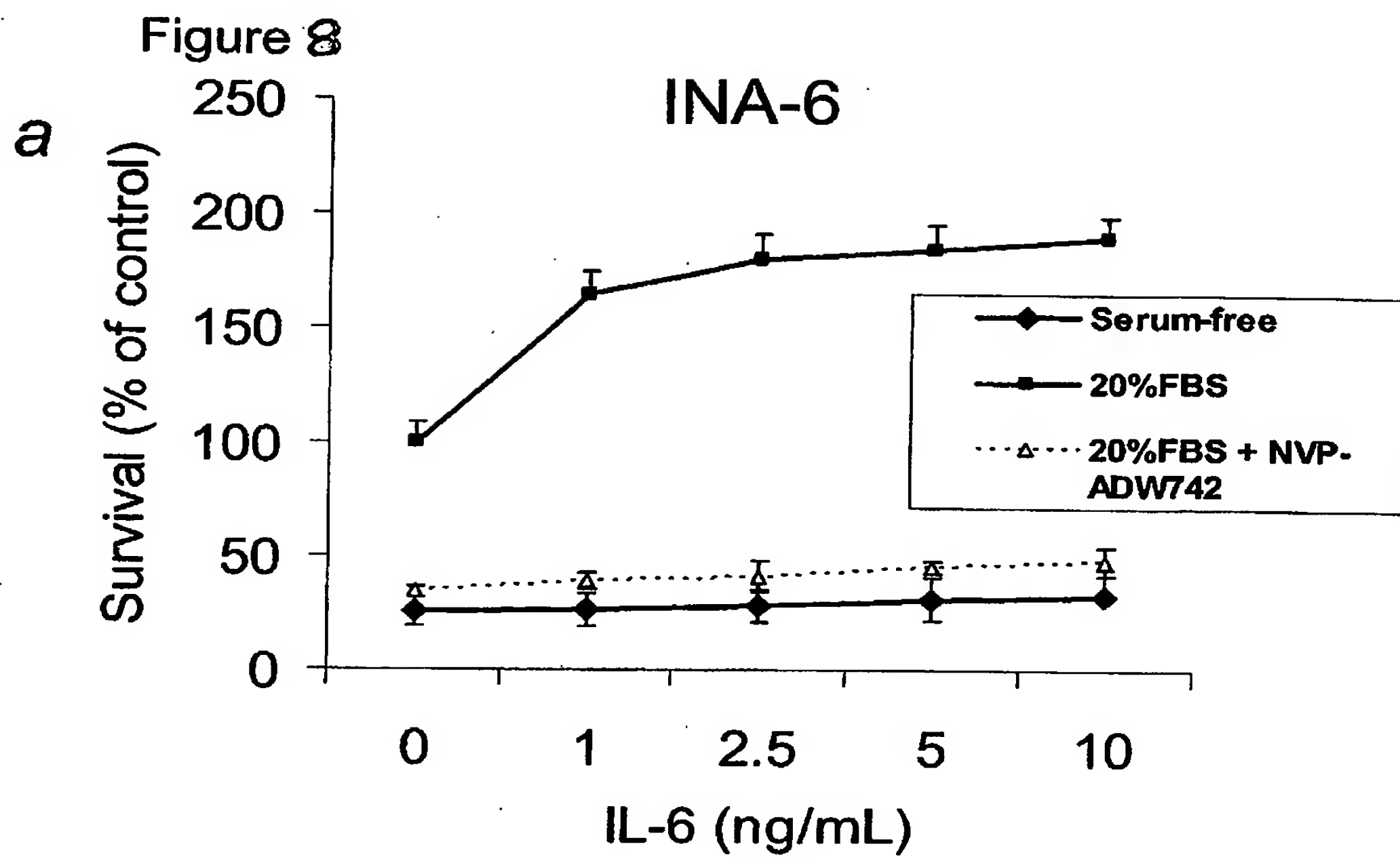


Fig. 9

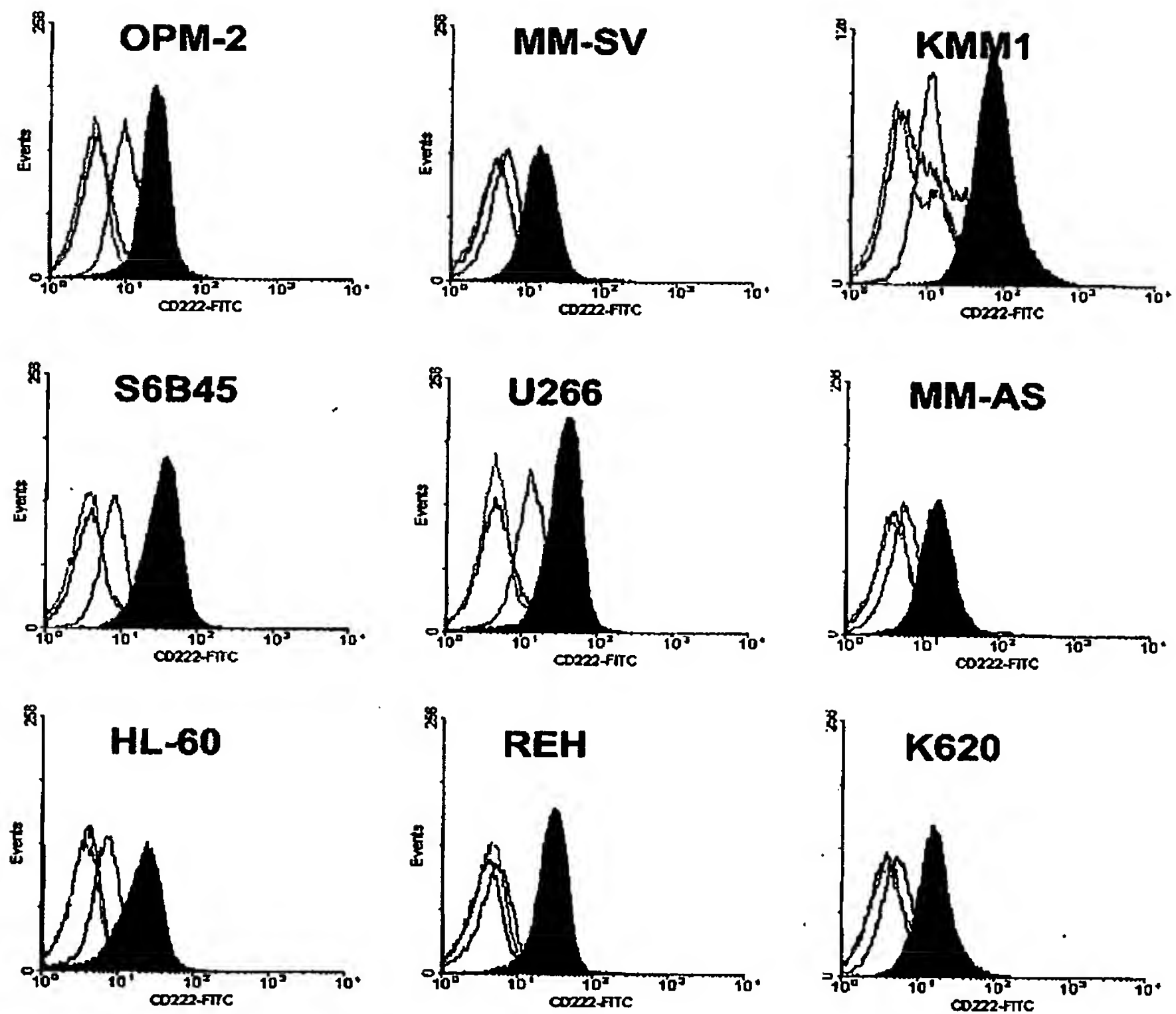


Figure 10

Transcriptional signature of IGF-1 stimulation

	Upregulated	Downregulated
Cell signaling	CK-1 and -2, chemokine-like factor 1, CXCR-4, Aurora-1, Aurora-2, SAK, SGK, PP2A, some PP1 subunits, PP4, GADD- α and - β , PTEN, CD71	FLIP, c-raf1 (but upregulated at protein level), Gas6, IGF-1, IGF-1R, IGF-2R, IFN- α , b, omega receptor, IL-2R γ , gp130, RAR- α , RAR- γ , BCMA, TNF- α -induced protein
Apoptosis regulation	Survivin, Bad, PCD5, PCD8, PCD10, VDAC3	Bcl-2 (no effect on protein level on short- to mid-term stimulation), Mcl-1 (stable protein levels), TOSO
Cell cycle control	Ki-67, CDC -2, -5, -6, -7, -20, -23, -25, -28, -45, cyclins A2, B1, B2, E1, F, G1, (D1, D2, D3), CDK2, CDK4, PCNA, replication factor C (multiple subunits), replication proteins A1, A2, and A3, ASK, CHK1, G2-S-expressed 1, stathmin/oncoprotein 1, Wee1+	
Microenvironmental interactions	RHAMM, Integrin α E, ADAM-8, -22, -28	Integrin α 8, α L, β 1, β 5
Wnt signaling pathway		Frizzled-related protein, WNT10B, WNT5B
Transcriptional/translational control	ATF-1, ATF-3, E2F-3, eIF-1, -2, -3, -4 and -5, multiple ribosomal proteins, DP-1, c-myc, XBP-1	c-myc
DNA synthesis/repair enzymes	BUB1, BUB3, DNA-PK, deoxycytidine kinase, deoxythymidylate kinase, DHFR, dyskerin, dUTP pyrophosphatase, MCM 2, 3, 4, 5, 6, 7, MSH-2, -3, -6, RAD51, guanine monophosphate synthase, RRM1, RRM2, TOPOIIA, XRCC	
Histone regulation	HDAC1, HAT1	
Oncogenes	DEK, liposarcoma fusion gene t(12;16), SET translocation	
Heat shock proteins / Chaperones	Hsp90, -70, 105, 27, 110, 14-3-3, chaperonin TCP1	
Immune system interactions		MHC class IE and II (less extensive changes in comparison to IL-6 or co-Cx)
Nucleocytoplasmic transport and other carrier proteins	Exportin, nucleoporins 50, 54, 62, 88, 98, 155, karyopherins b1, b3, a1, a2, a3, a4, kinesin-like 1, 2, 4, 5, 6, 7 (multiple Rab, Ran proteins), transportins	
Metabolism	F0F1 ATPase mitochondrial, ornithine decarboxylase, HMG-CoA reductase, calmodulin-1 and -2	
Ubiquitin/Proteasome pathway	POH, Multiple 26S subunit genes (26S subunits α 1, α 2, α 3, α 5, α 7, β 1, β 2, β 3, β 5, β 6, β 7, β 8, ATPase 1,2,3,4,5,6, non-ATPase 1,2,4,7,8,11,12,13), UCEs, USPs	Some USPs (-9, -11)

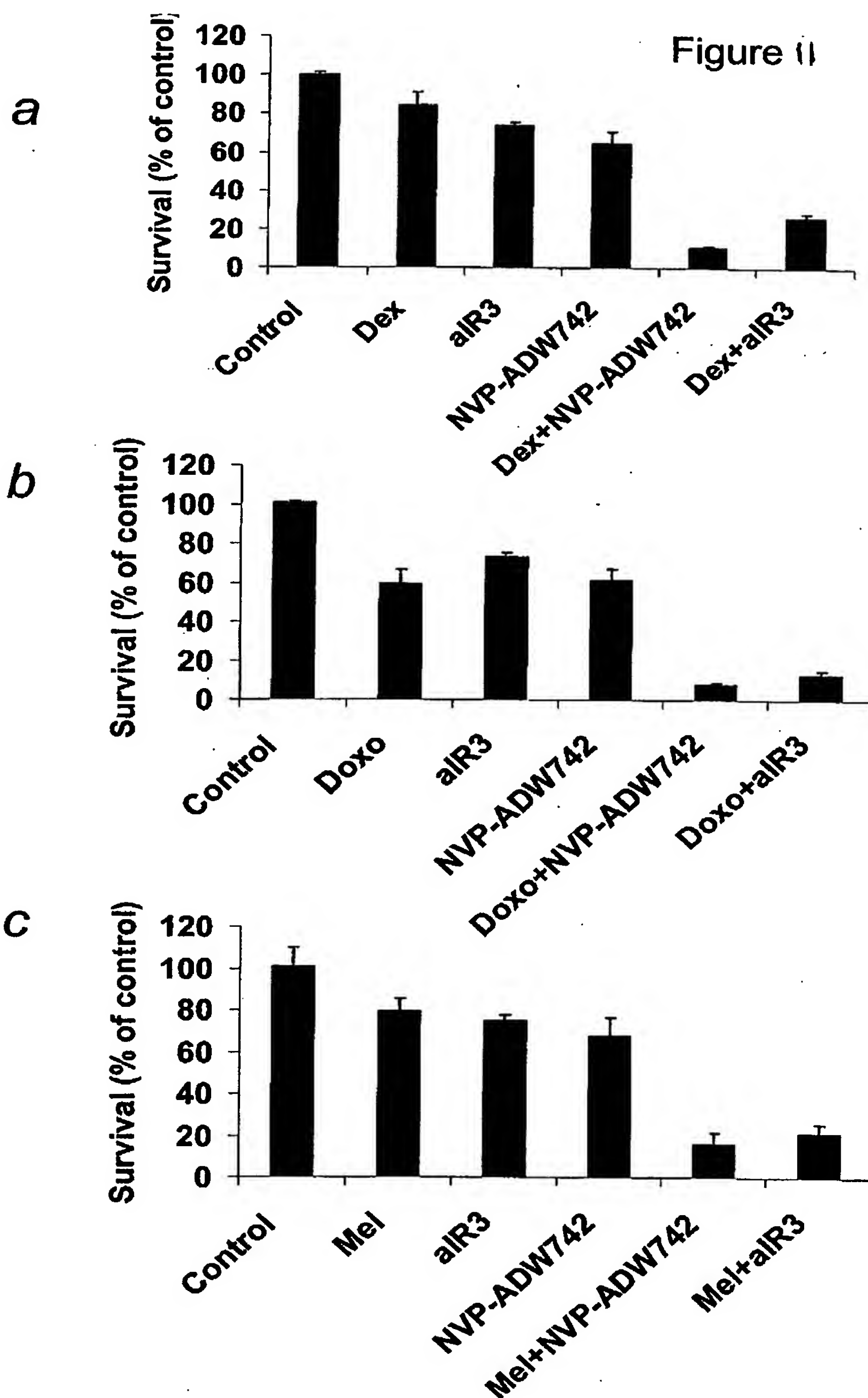


Figure 12

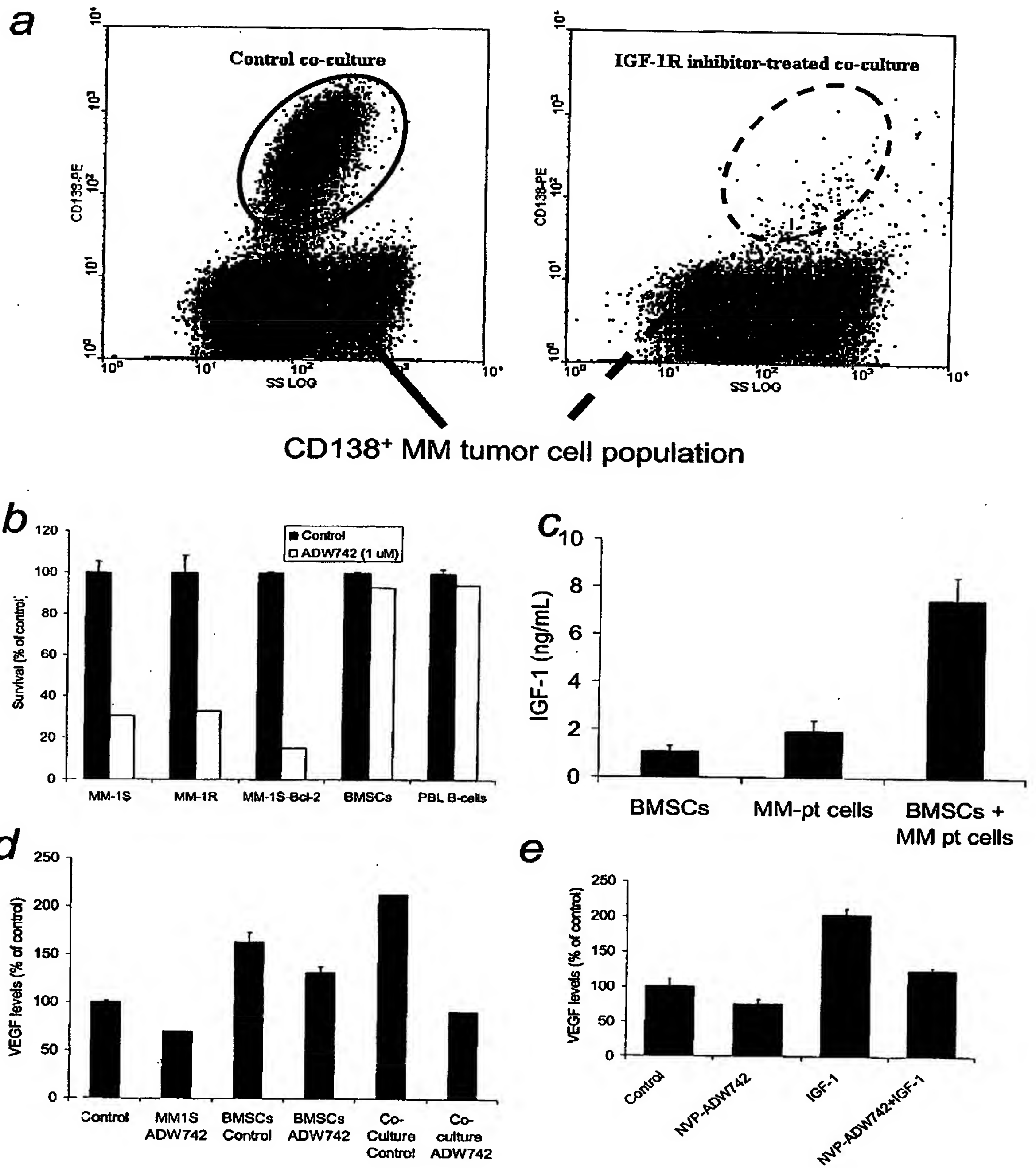


Figure 13

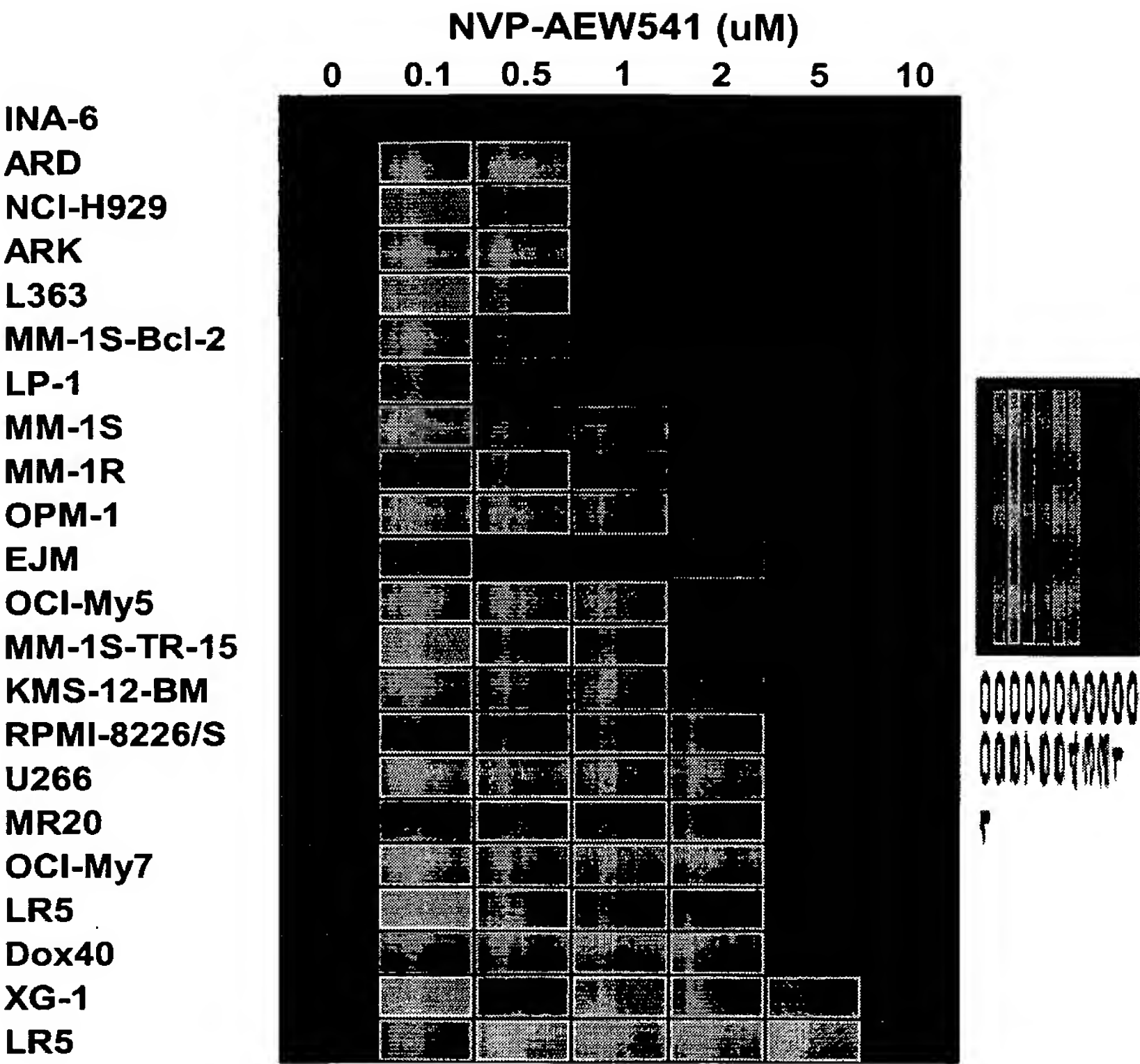


Figure 14

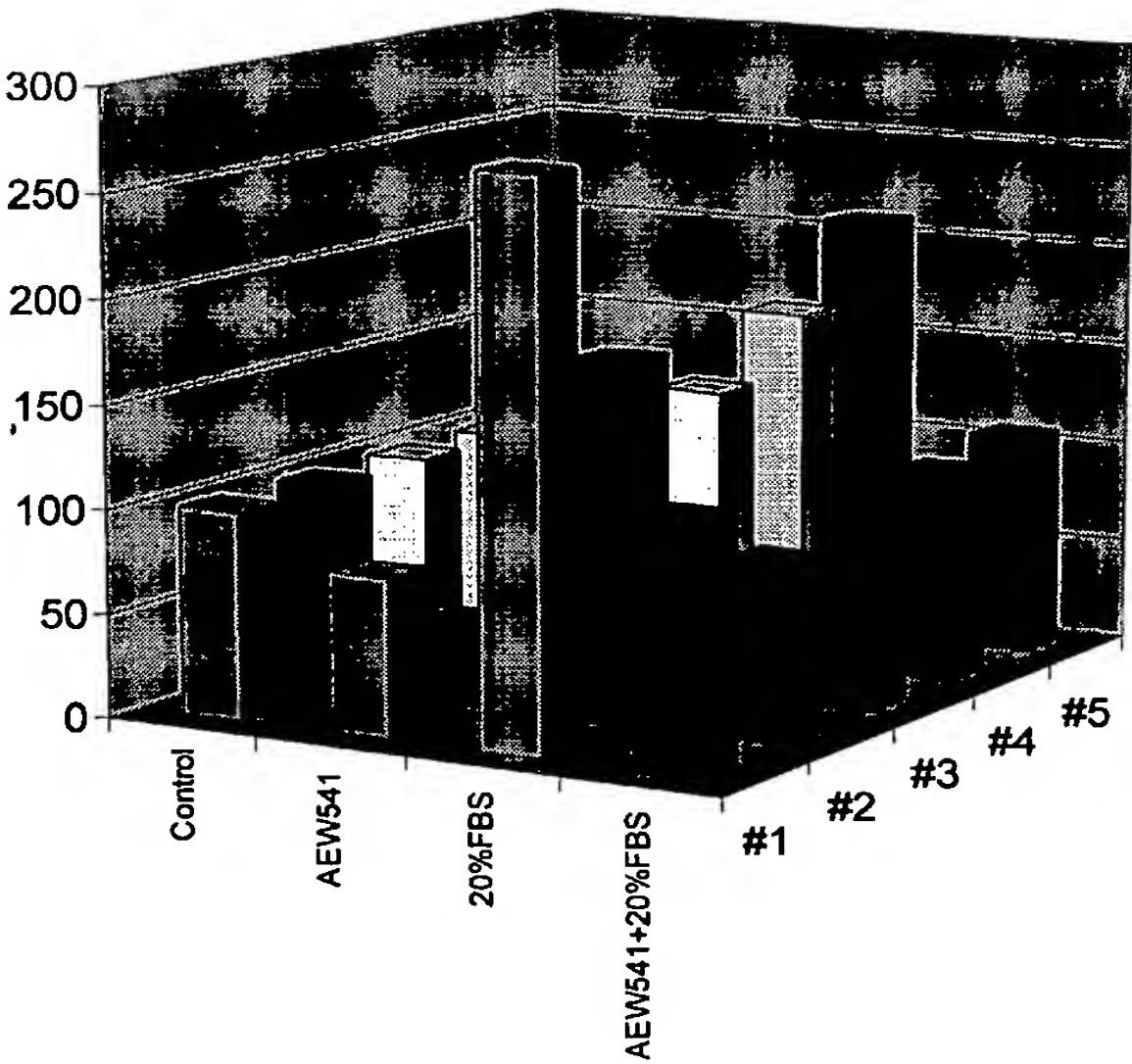


Figure 15

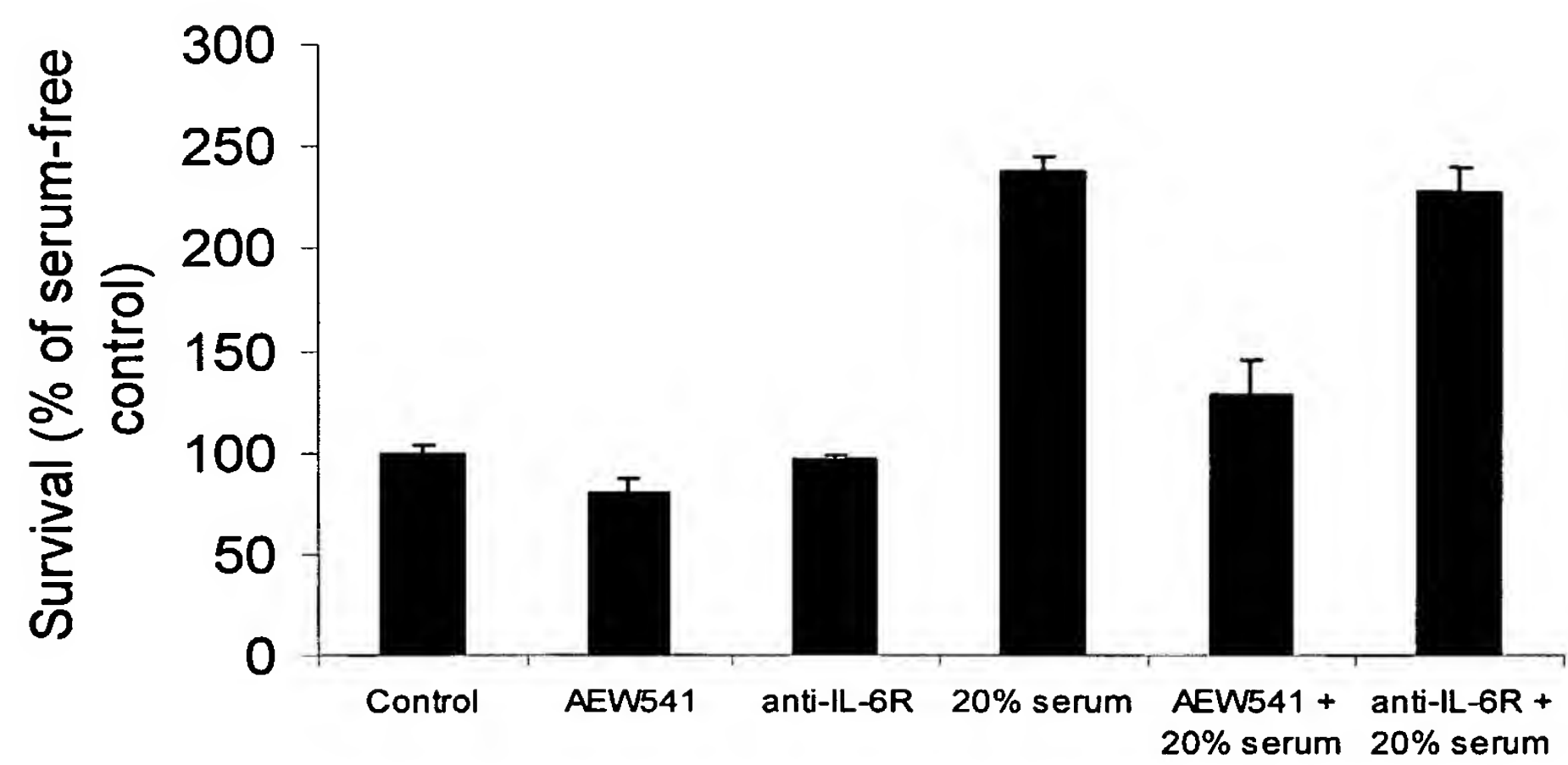


Figure 16

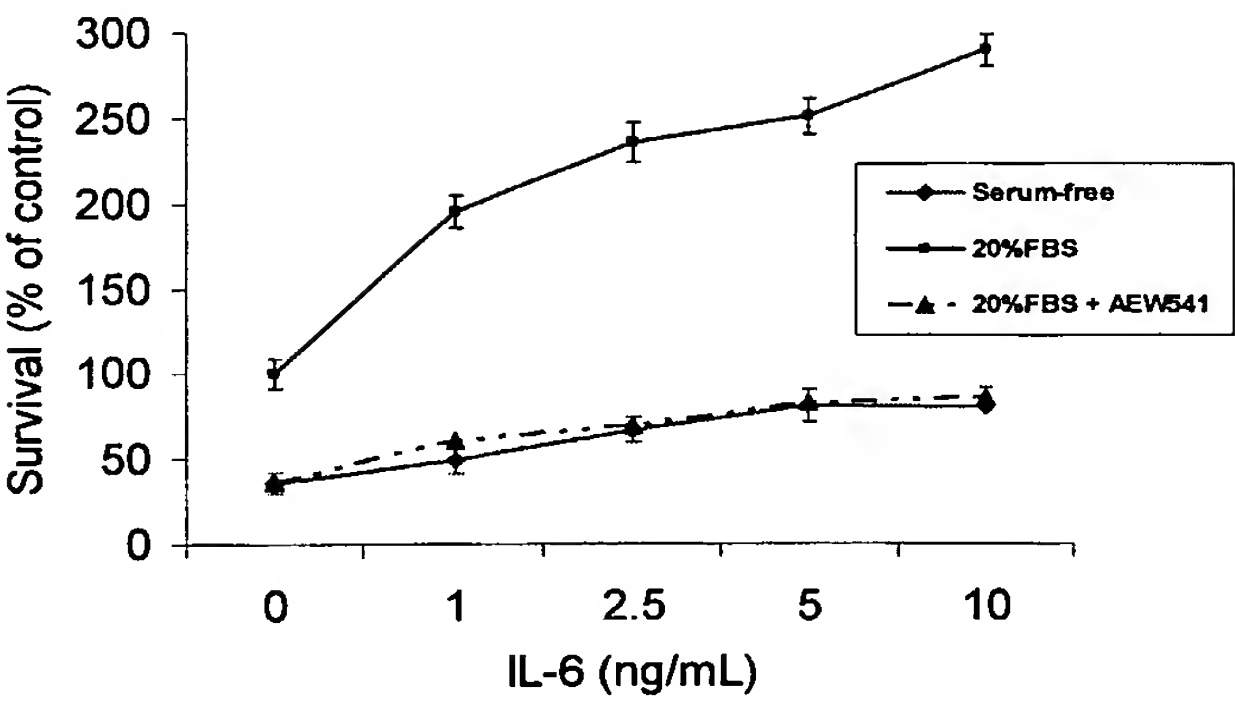


Figure 17

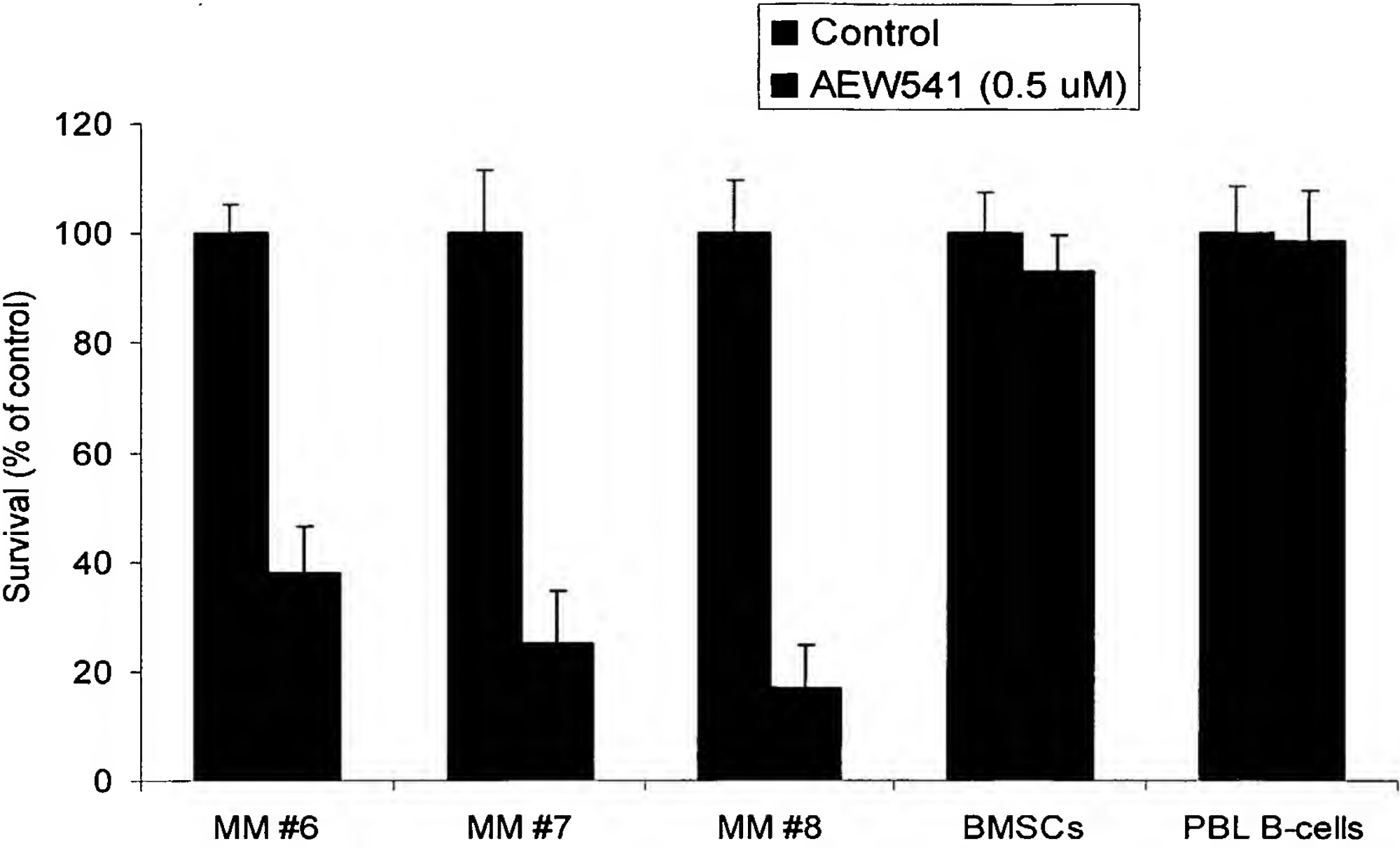


Figure 18

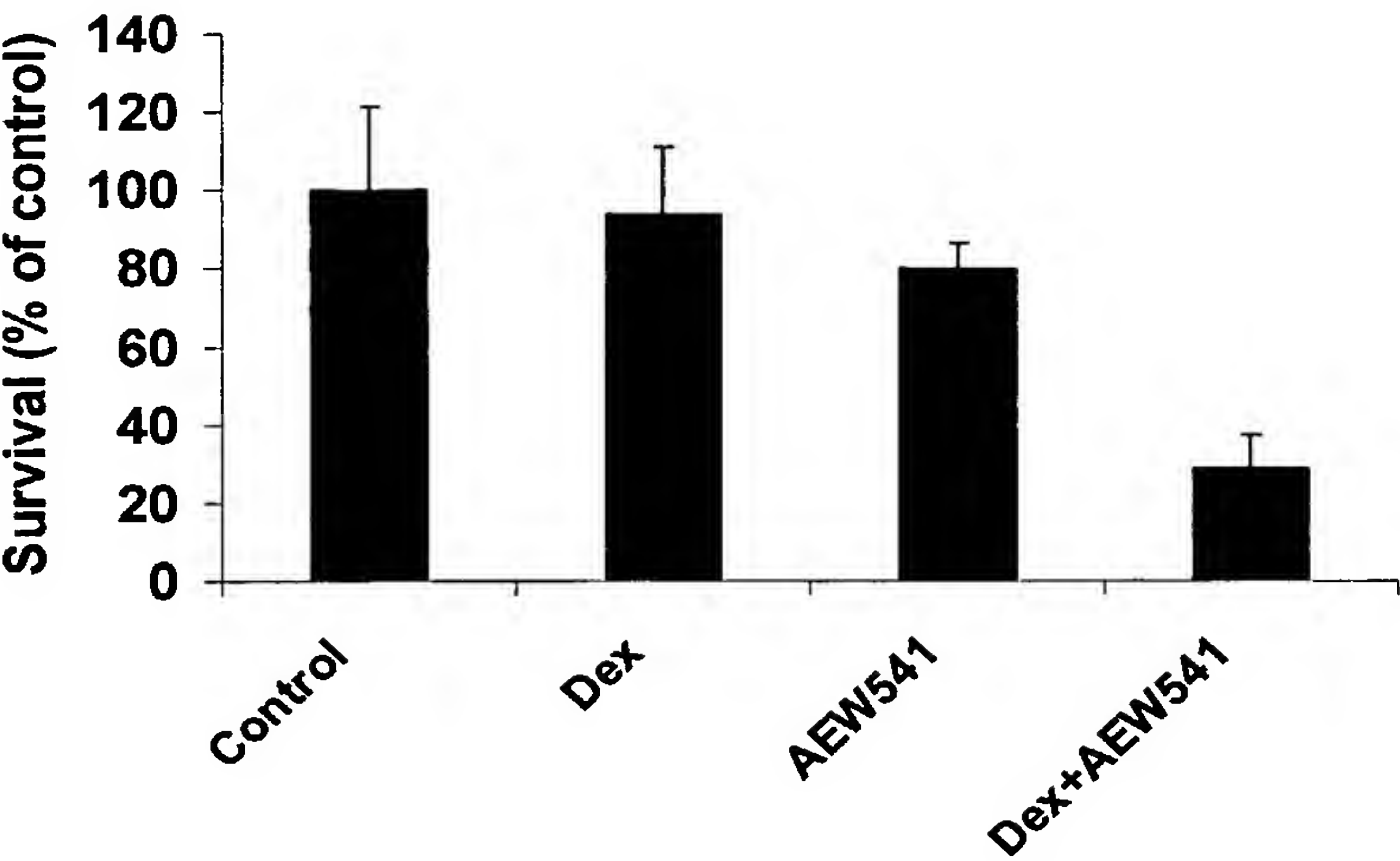


Figure 19

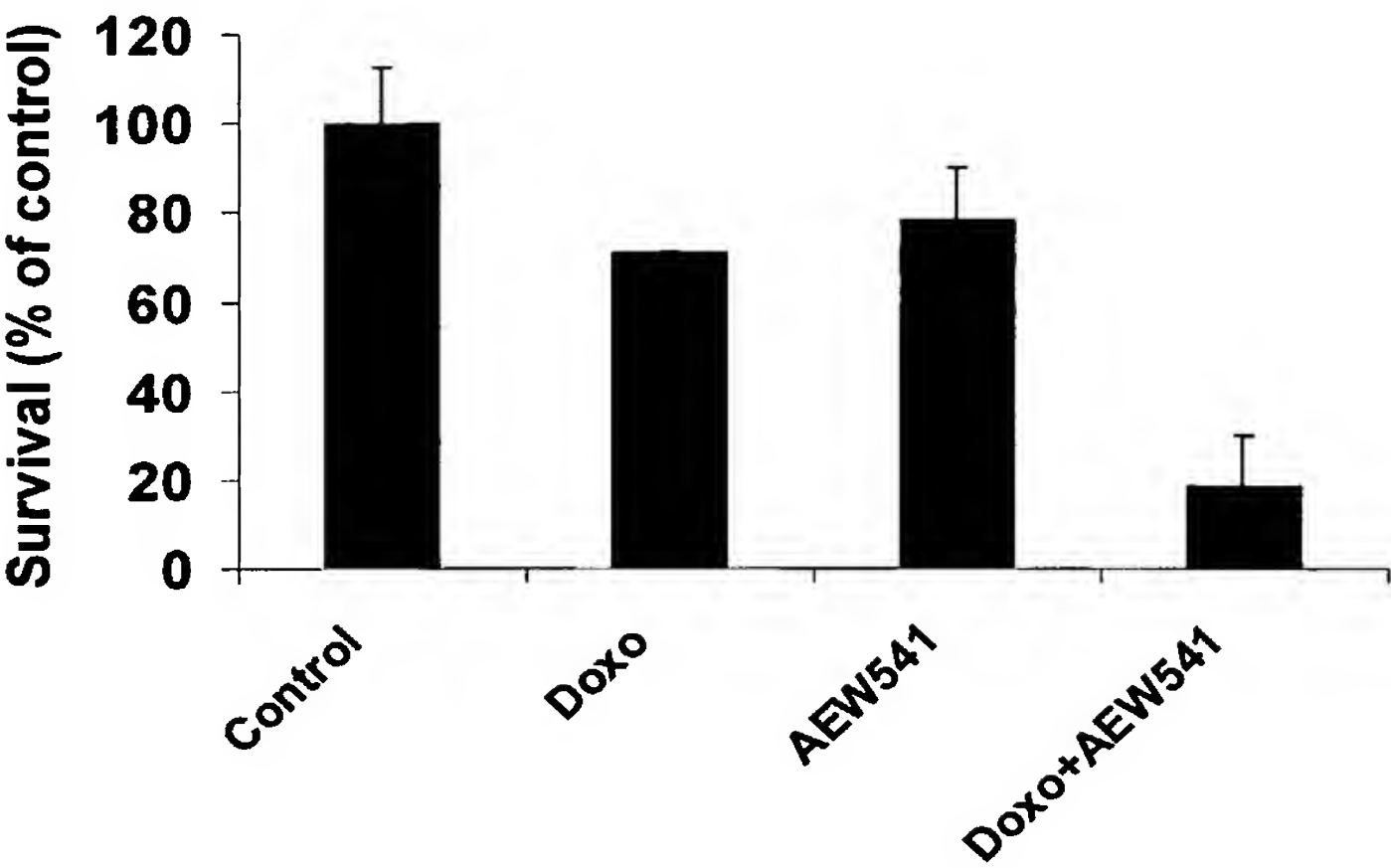
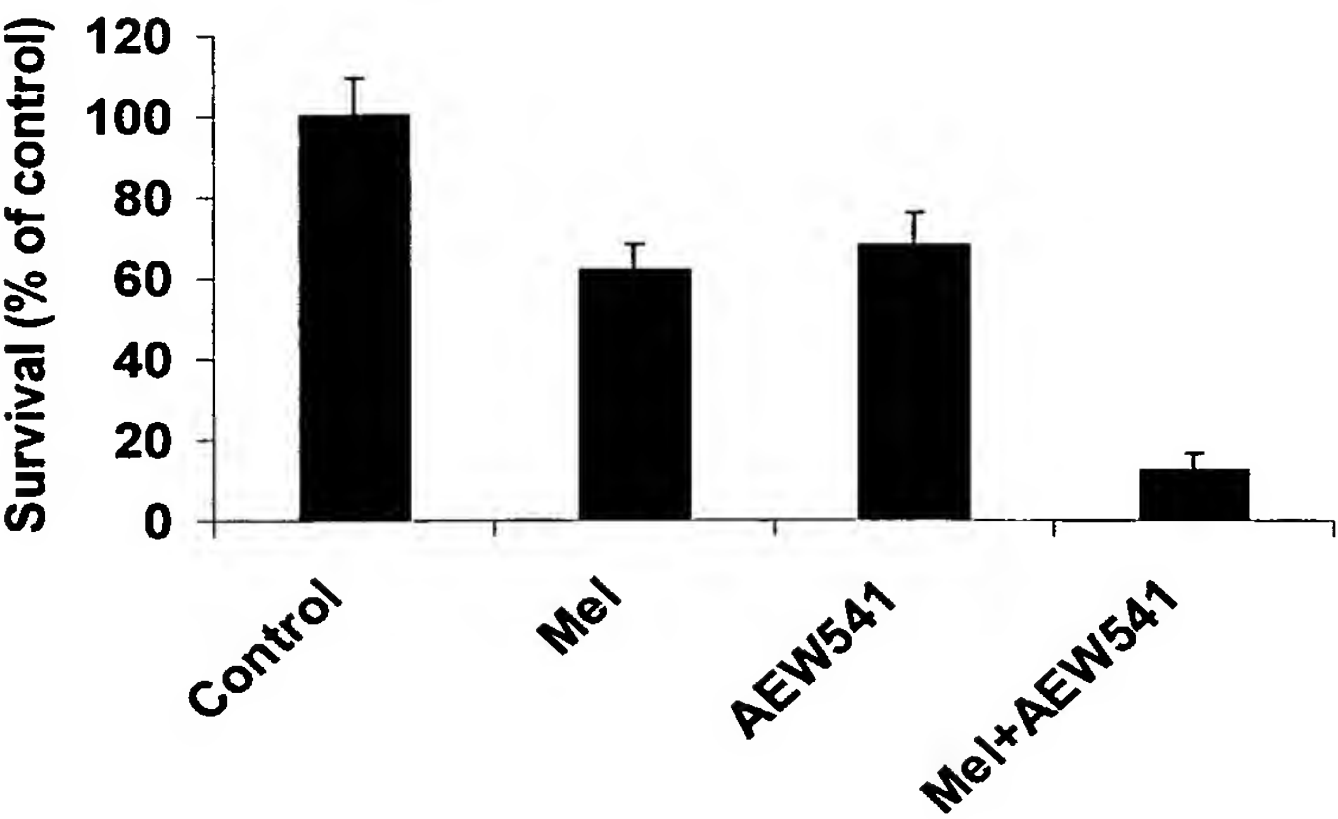


Figure 20



21/30
21/30

Figure 21

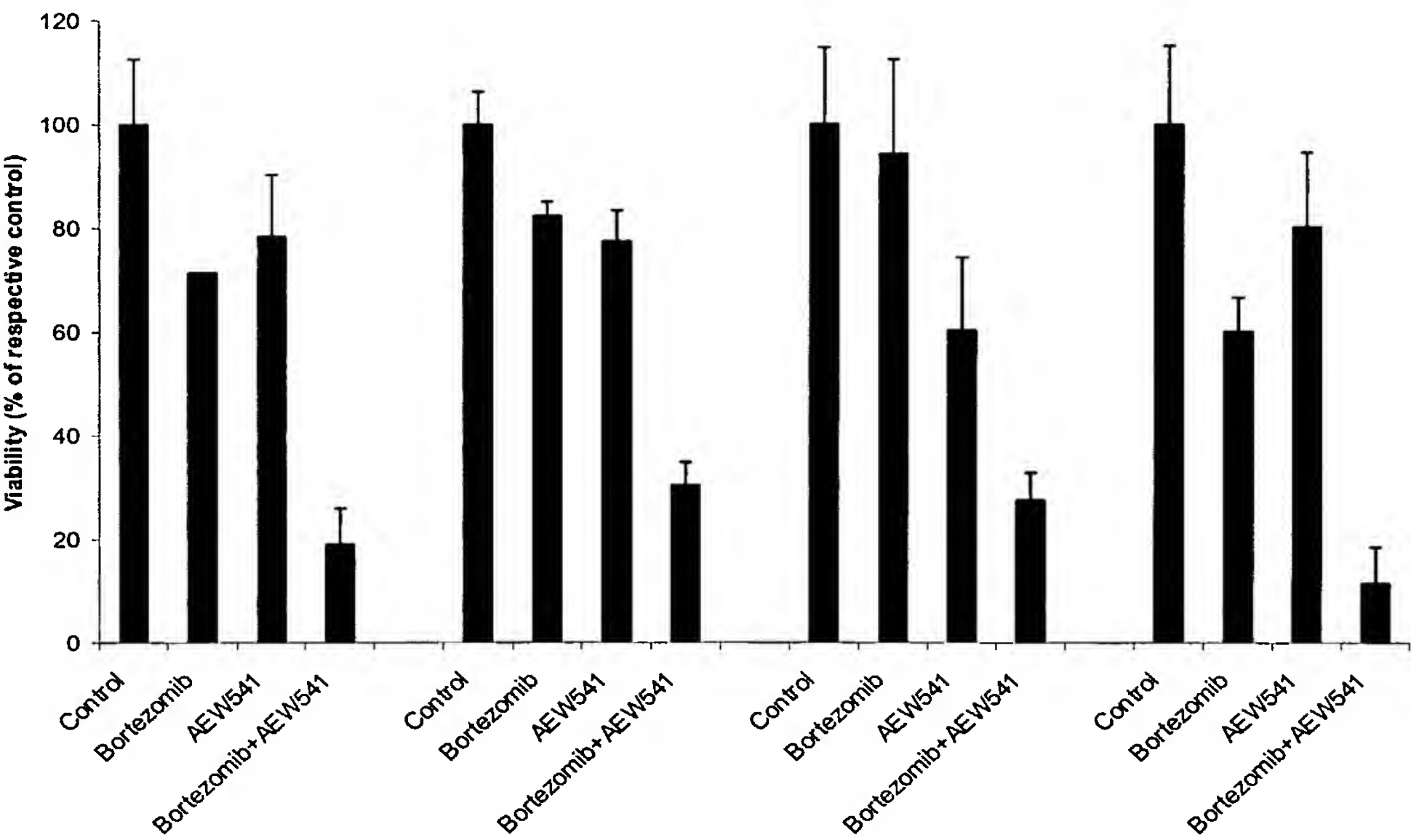


Figure 22

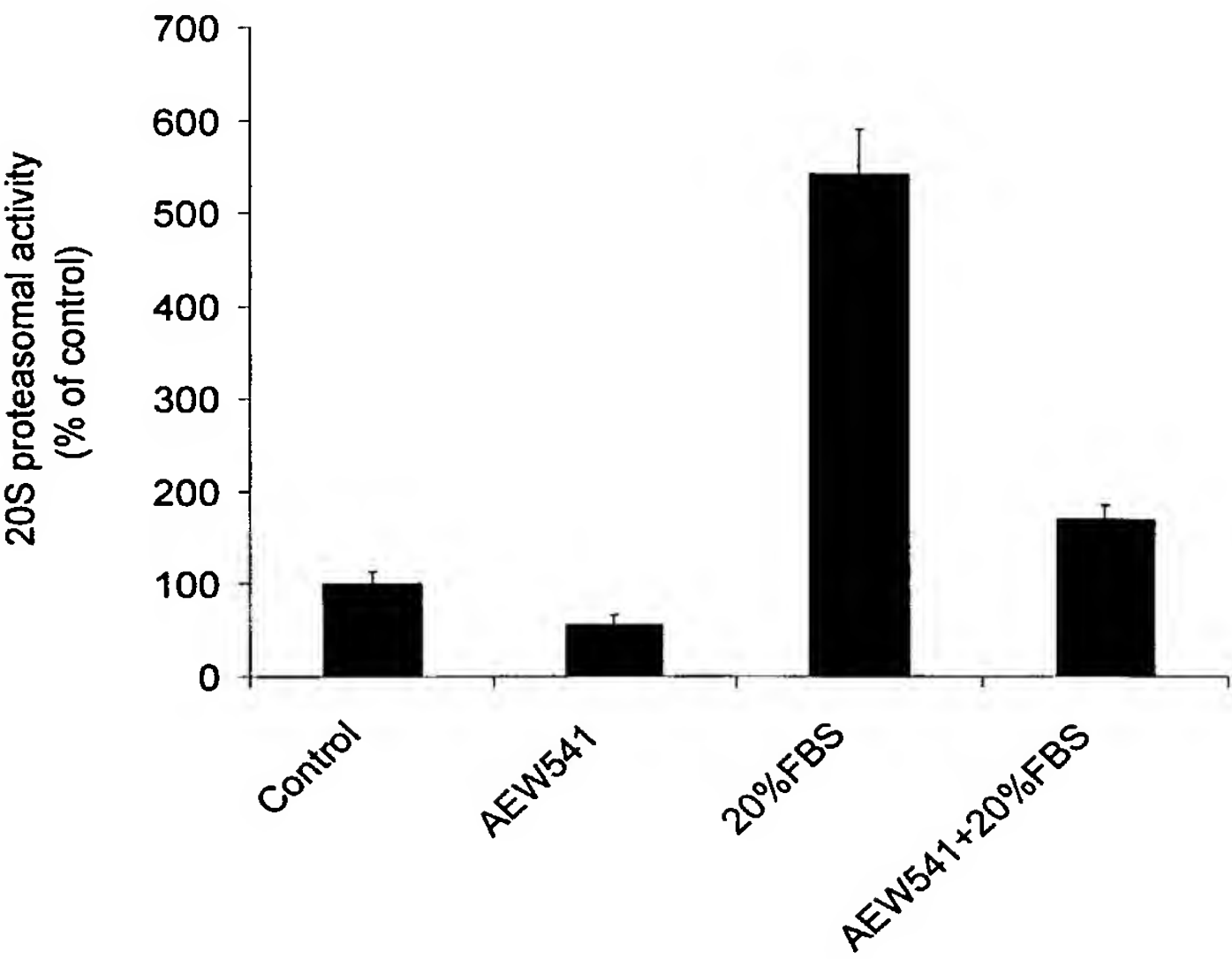


Figure 23

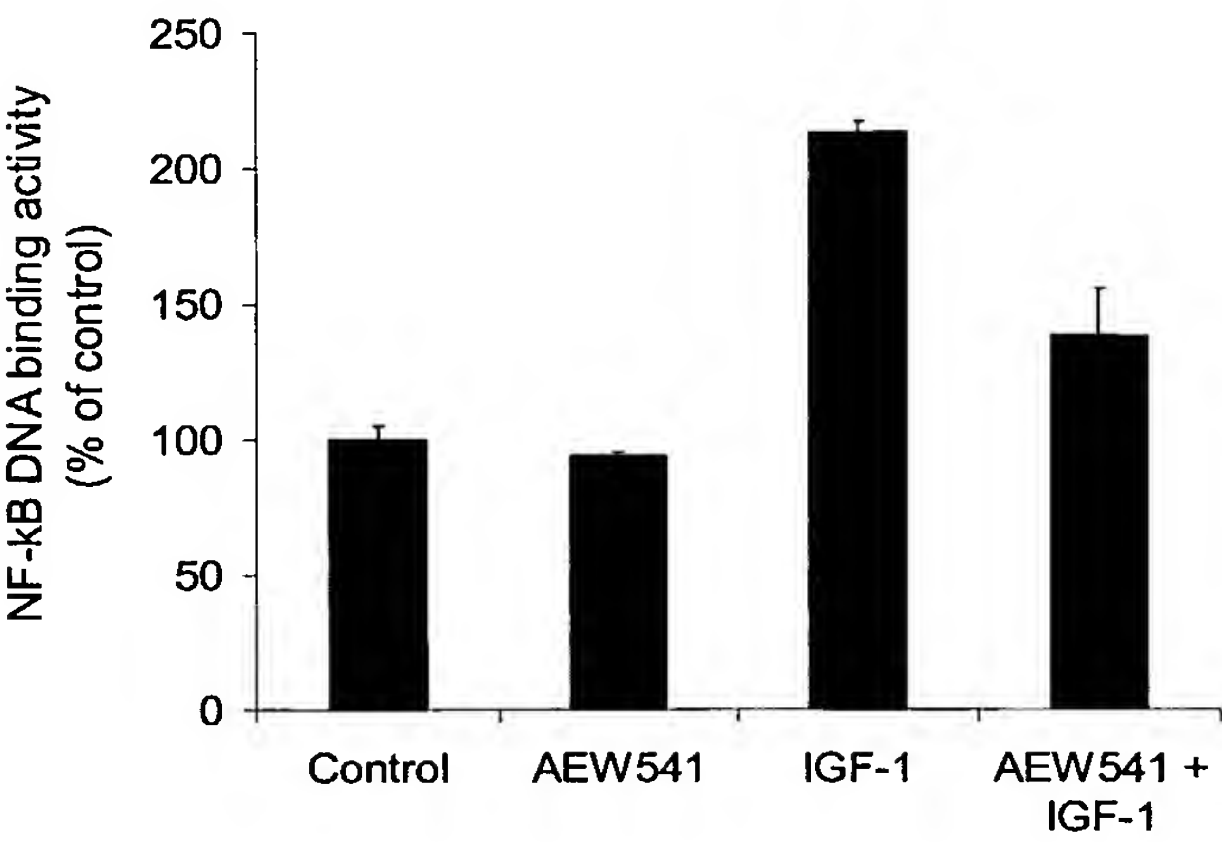


Figure 24

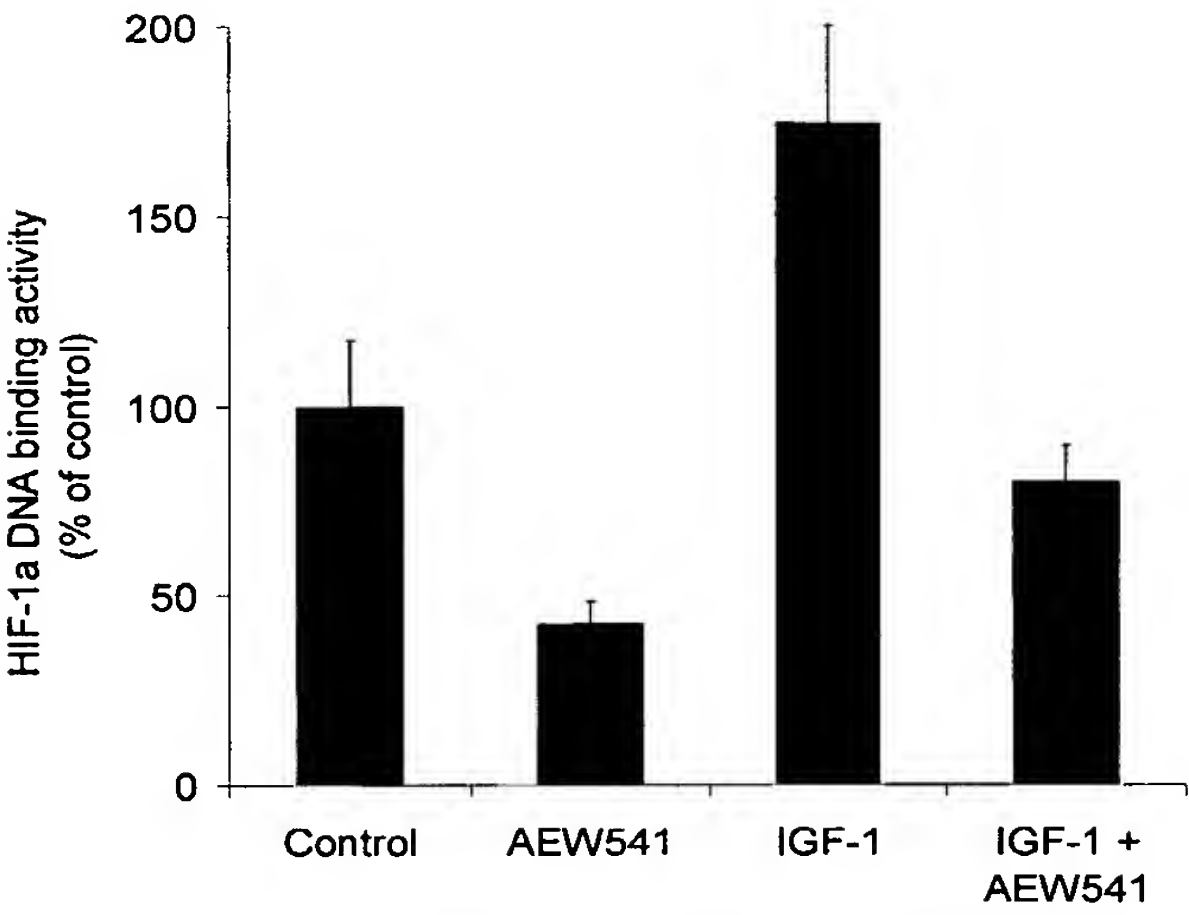


Figure 25

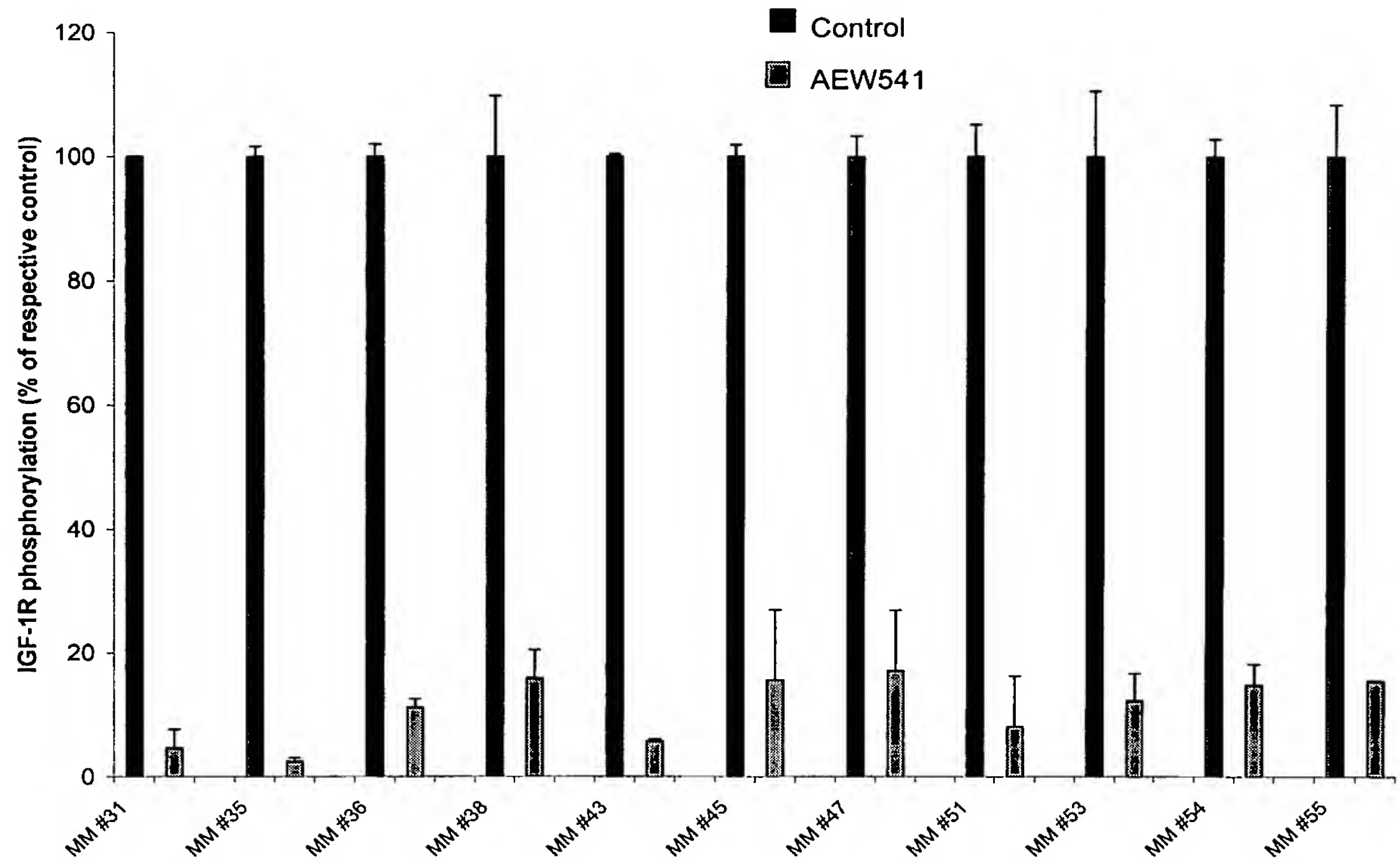
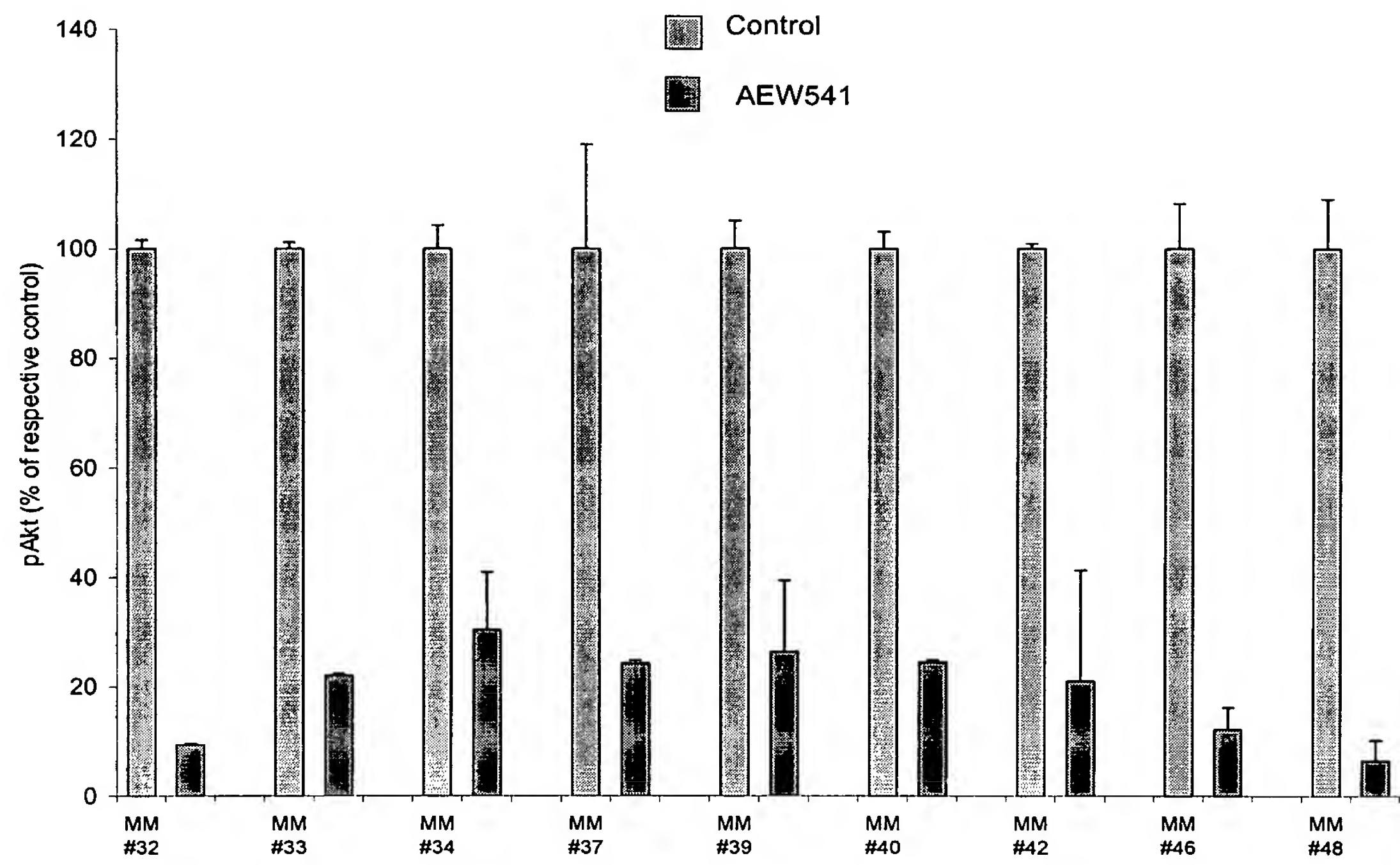


Figure 26



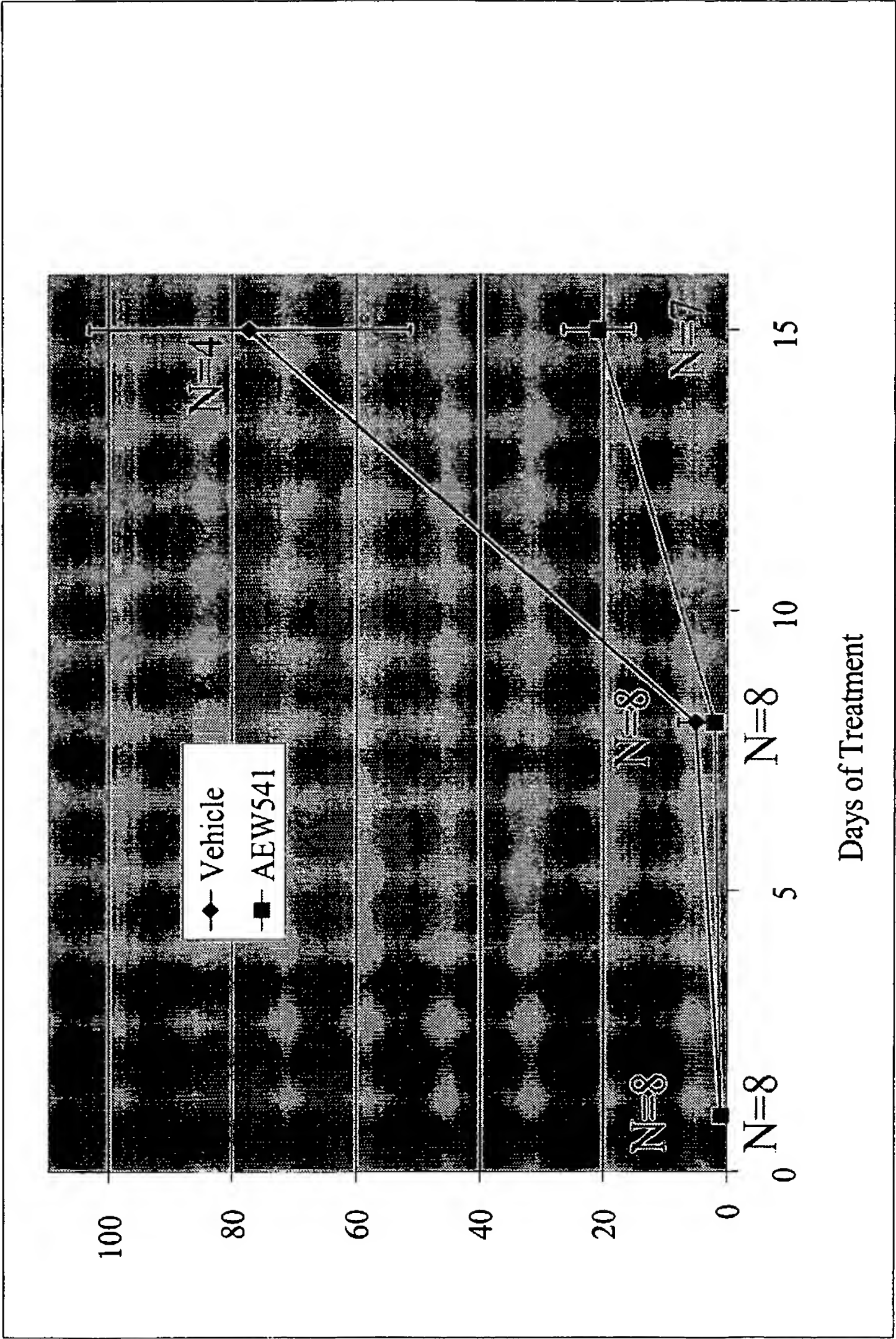


Figure 27

Figure 28

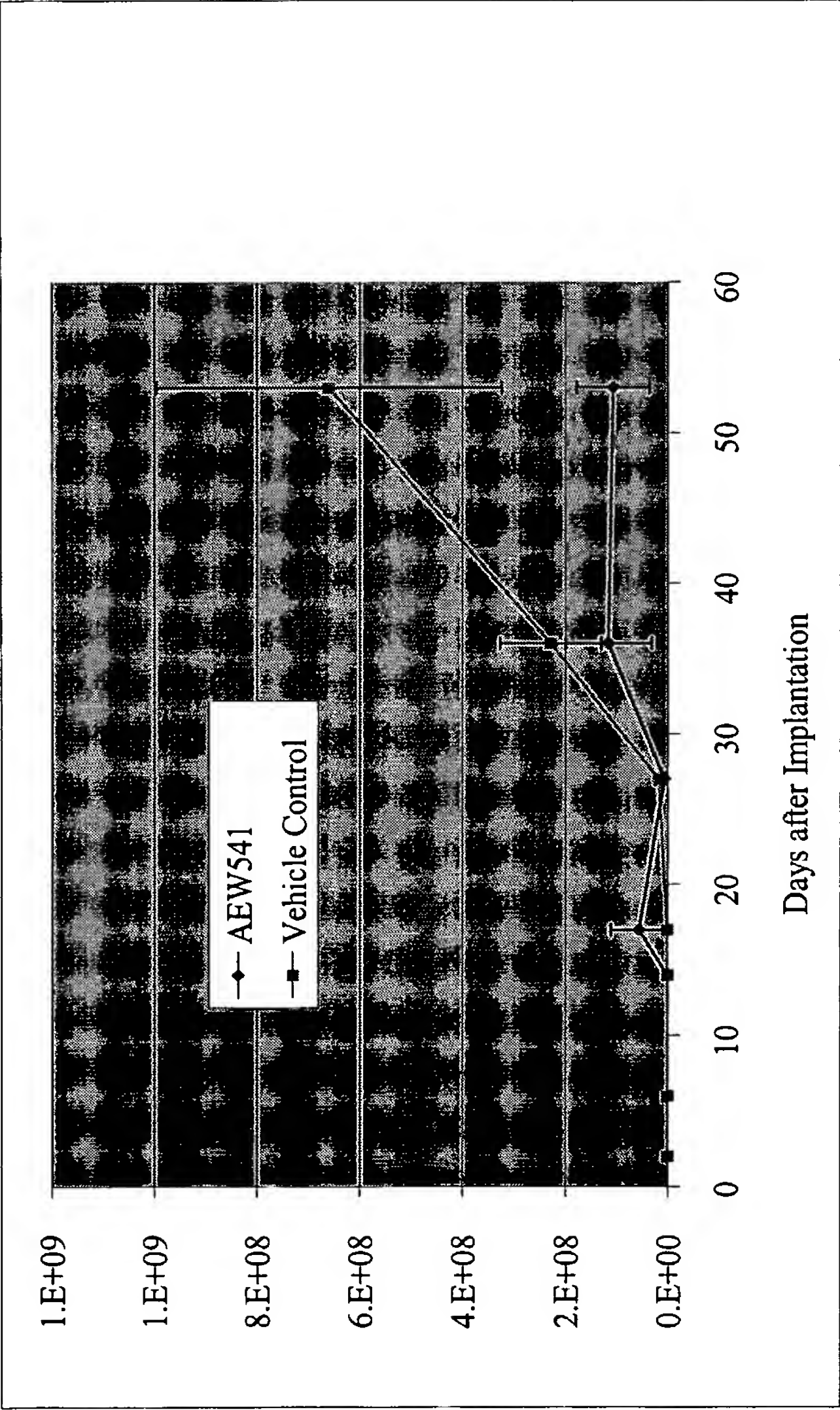


Figure 29

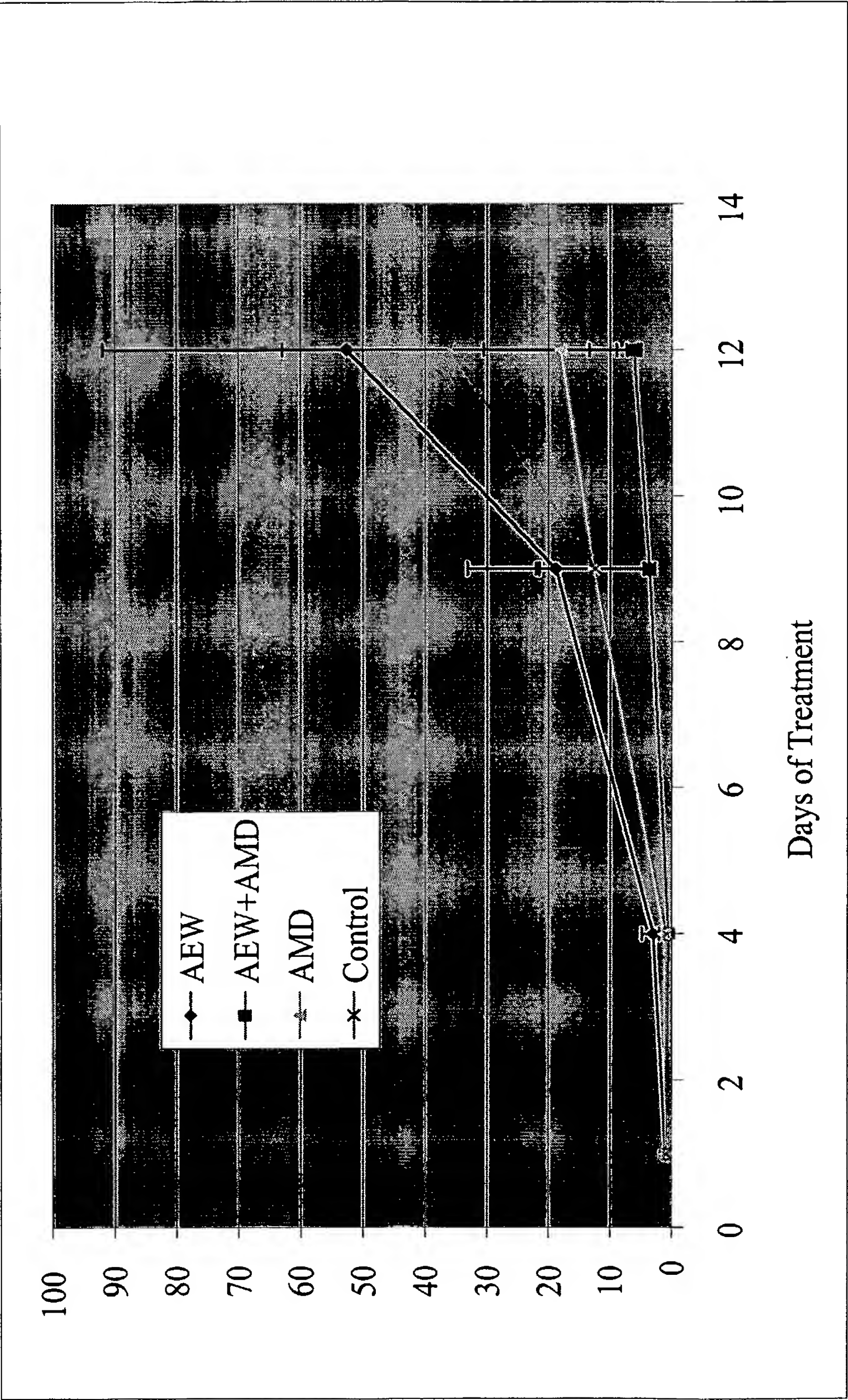
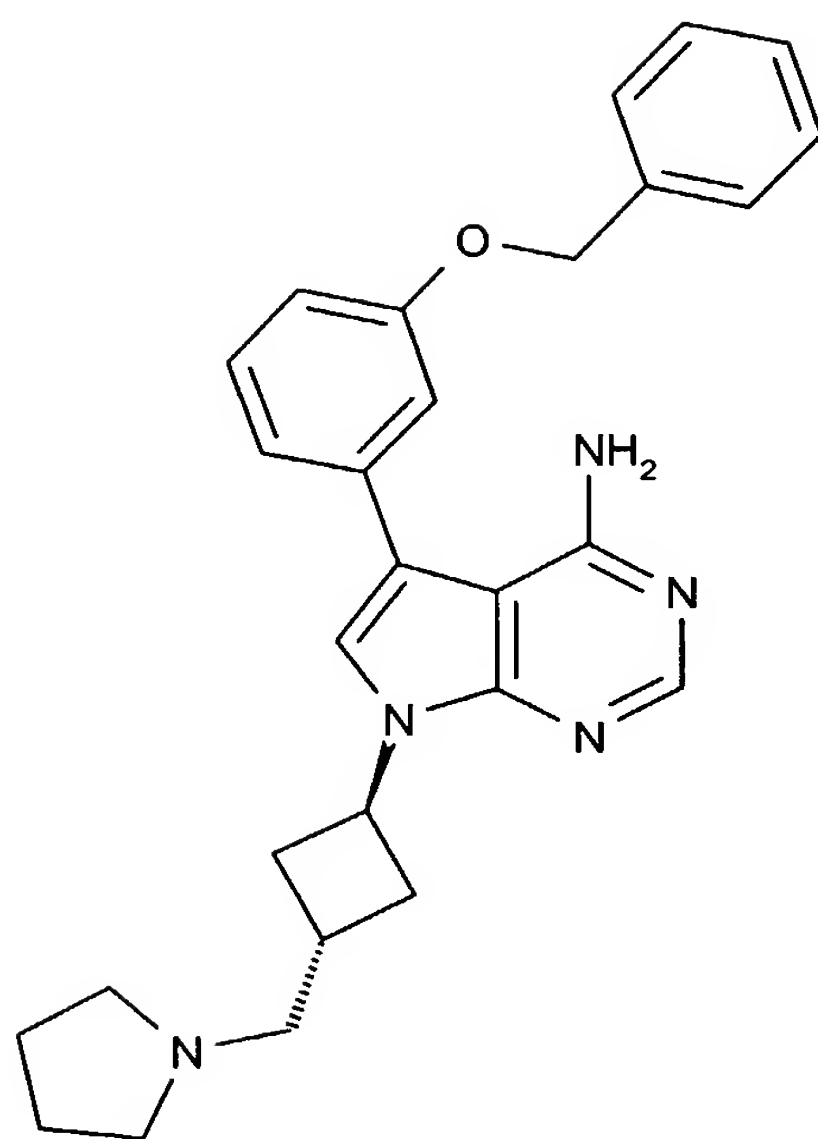
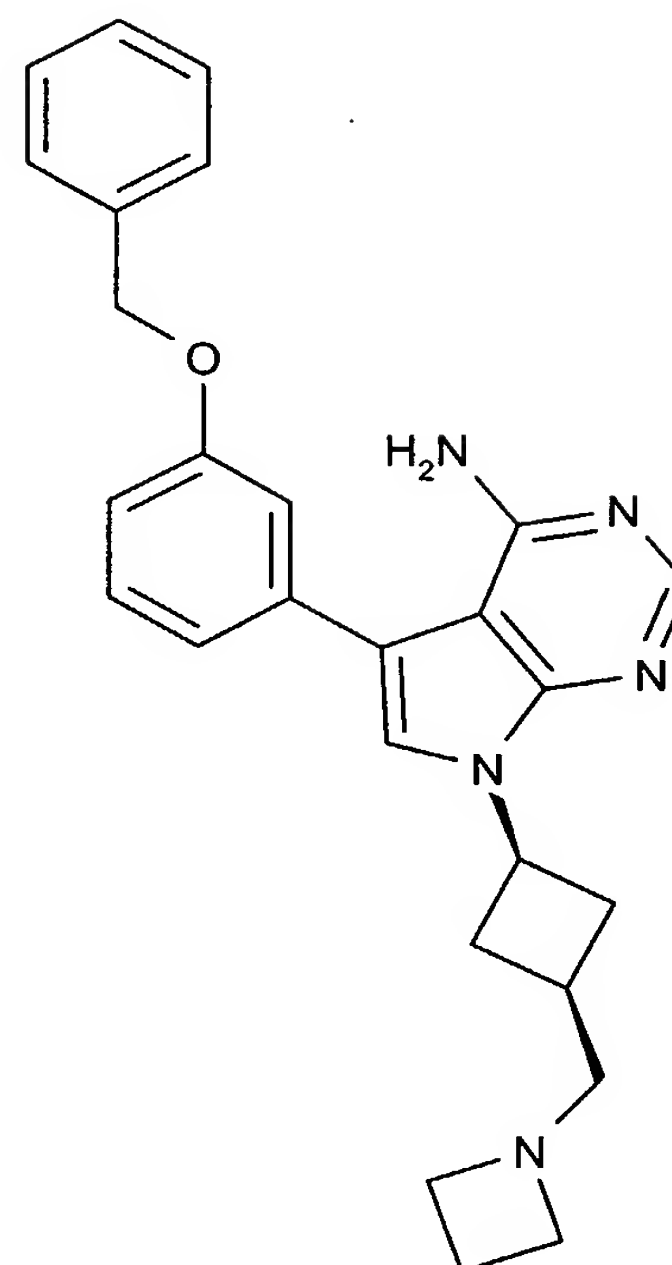


Figure 30

**ADW742**

**5-(3-Benzyloxy-phenyl)-7-(3-pyrroli
din-1-ylmethyl-cyclobutyl)-7H-pyrro
lo[2,3-d]pyrimidin-4-ylamine**

**AEW541**

**7-(3-Azetidin-1-ylmethyl-cyclobutyl
) -5-(3-benzyloxy-phenyl)-7H-pyrrolo
[2,3-d]pyrimidin-4-ylamine**